Aus der Klinik für Anästhesie und Intensivtherapie

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in Zusammenarbeit mit dem Universitätsklinikum Gießen und Marburg GmbH,
Standort Marburg

Pharmacokinetics of paracetamol (Perfalgan®) following different infusion protocols in a porcine model.

Inaugural-Dissertation zur Erlangung des Doktorgrades der gesamten Humanmedizin

dem Fachbereich Medizin der Philipps-Universität Marburg vorgelegt

von
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aus Lahore, Pakistan

Marburg 2008

Angenommen vom Fachbereich Medizin
der Philipps-Universität Marburg
am 06.10.2008

Gedruckt mit Genehmigung des Fachbereichs

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Meinen Eltern in Liebe und Dankbarkeit

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ABBREVIATIONS

ACTM	**Ac**et**am**inophen
AUC	**A**rea **U**nder the **C**urve
C(max)	maximum plasma concentration
CB	**C**anna**b**inoid
Cl(t)	total clearance
CNS	**C**entral **n**ervous **s**ystem
COX	**C**yclo**ox**ygenase
COX-2	**C**yclo**ox**ygenase-**2**
COX2- inhibitors	**C**yclo**ox**genase-**2**- inhibitors
CSF	**C**erebro**s**pinal **f**luid
i.v	Intravenous
MRT-tot	**M**ean **R**esident **T**ime total
NMDA	**N**-**m**ethyl **D**-**a**spartate
NO	**N**itric **o**xide
NSAIDs	**N**on-**s**teroidal **a**nti-**i**nflammatory **d**rugs
PBD	**P**article-**b**ound **d**rug
pKa	dissociation constant
SD	**S**tandard **D**eviation
t 1/2 alpha	distribution half-life
Teq	**eq**uilibration half-**t**ime
TopFit	**T**homae **O**ptimized **P**harmacokinetic **F**itting **P**rogram
Vd(ss)	**V**olume of distribution at equilibrium

1. Introduction

Adequate treatment of pain in the post operative period is essential to avoid unnecessary distress and to minimise the potential complications (Mackintosh, 2007).
There have always been attempts to improve the management of pain treatment but, the management of post operative pain still needs improvement. Clinical, psychological and institutional consequences may arise from inadequate pain management (Hutchison, 2007). The unsatisfactory treatment of post operative pain can be the result of a unimodal therapy (Kehlet & Dahl, 1993). By combining pharmacological management and other measures, strategies should be developed to ensure maximum pain relief for each patient (Mackintosh, 2007). A multimodal or "balanced analgesia" appears to be the key for successful transition between anaesthesia and post-operative analgesia (Joris *et al.*, 2001). The intra-operative use of various adjuvant therapies that reduce the need for opioid and/or post-operative pain severity is an important part of balanced analgesia. The application of opioid- and non-opioid analgesics according to their pharmacokinetic characteristics, facilitate the transition from anaesthesia to analgesia (Joris *et al.*, 2001). The advantages of balanced analgesia are based upon the fact that due to the additive or synergetic effects of different analgesics, an optimal analgesia can be achieved with minimal doses of individual therapeutic agents; it leads to the reduction of side effects (Kehlet & Dahl, 1993). A combination of opioid and non-opioid analgesics e.g. paracetamol is usually used as balanced analgesia.

Paracetamol is an active metabolite of phenacetin and belongs to the group of non opioid analgesics. It exerts its analgesic effects by the peripheral and central inhibition of prostaglandins. The mechanism of action of paracetamol analgesia is not clearly understood but, it involves multiple factors. It is a potent inhibitor of prostaglandin synthesis with in the central nervous system (Piletta *et al.*, 1990). Similarly it interferes with nociception associated with spinal NMDA (Bjorkman, 1995) receptor activation. This effect involves the

inhibitory action on spinal nitric oxide (NO) mechanisms (Bjorkman, 1995). Paracetamol is available as an oral, rectal and newly developed as an intravenous (Hahn *et al.*, 2003) applicable form. The i.v. application of paracetamol avoids variability associated with gastric absorption and first-pass hepatic metabolism (Back & Rogers, 1987), resulting in higher plasma concentration and greater analgesic efficacy than orally administered drug. The oral administration results in an unpredictable variation in plasma concentration compared with i.v. administration (Holmer *et al.*, 2004). Moreover after a number of surgical procedures (intestinal, head and neck surgeries etc.), enteral application of analgesics is not possible. In such cases i.v. paracetamol is a good alternative to non-steroidal anti-inflammatory drugs (Graham *et al.*, 1999) and other non-opioid analgesics. Intra-operative administration of paracetamol has been shown to decrease pain with a morphine sparing effect (Binhas *et al.*, 2004).

There are two intravenous inject able forms of Paracetamol. The water soluble, inject able form Propacetamol; that is rapidly hydrolyzed to acetaminophen (paracetamol) in the blood by the enzymatic action of esterases. Hydrolysis of 2 g Propacetamol yields 1 g paracetamol (Bannwarth *et al.*, 1992d; Flouvat *et al.*, 2004).

The second inject able form is a direct intravenous inject able form of paracetamol (e.g. Perfalgan®).1g of Paracetamol administered as Perfalgan®
10 mg/ml is bioequivalent to 2 g Propacetamol with a better local safety. Perfalgan® is a ready-to-use formulation and must not be reconstituted in to a solution as Propacetamol (Flouvat *et al.*, 2004).
These studies indicate an optimal bioavailability of paracetamol by intravenous application and the synergetic effects to Cyclooxgenase-2-inhibitors (COX2- inhibitors) are reported which can be partly replaced by paracetamol and the low incidence of side effects makes i.v. paracetamol a good alternative drug for other analgesics.

The recommended dosage for the intravenous application of Perfalgan® is an infusion of 1g over 15 minutes. The aim of our study was to evaluate the pharmacokinetics of i.v. paracetamol after different infusion rates and in view of the results the optimization of dosage and mode of i.v. application of paracetamol.

1.1 Non-opioid analgesics

Antipyretic analgesic were developed about a hundred years ago and divided in to two groups; the acidic (aspirin-like drugs) and non-acidic (acetaminophen-phenazone-like) compounds (Brune & Neubert, 2001). The analgesics having a pKa-value (that is the pH- value at which the 50 % of the substance is found to be in dissociated form) of less than 5 are called acidic-antipyretic-analgesics and those with a pka value of more than 5 are the non-acidic analgesic-antipyretics.
Acidic- and non-acidic antipyretic analgesics possess different pharmacokinetic properties. The acidic-antipyretic-analgesics achieve high concentrations in tissues with low pH like inflamed tissue, which is assumed to account for their superior anti-inflammatory potency and also reach comparatively high concentrations in the stomach wall, kidney cortex and blood, resulting in the well-known side effects that occur with acidic compounds but not with paracetamol and phenazone (Brune & Neubert, 2001).

The non-acidic-group is further divided into chemical groups of pyrazolinone and aniline. The example of pyrazolinone includes Metamizol; and paracetamol belongs to the aniline group.

Another group of non-narcotic-antipyretic-analgesics includes the cyclooxygenase- (COX-) 2-inhibitors. The examples include Celecoxib, Etoricoxib and Parecoxib.

1.2 History

In the ancient history from Egypt and Greece, the analgesic and antipyretic effects of willow bark are known for centuries. The modern era of salicylates starts from 1758 with a report by Edward Stone (“an account of the success of the bark of willow in the cure of agues”) sent to The Royal Society in London. The active ingredient of willow bark “salicine” was first isolated in 1828 by Joseph Buchner, then by Henri Leroux, and also prepared from the oil of wintergreen (Gualtheria) and meadowsweet (Spirea ulmaria) by J.W.Lowig 1833, called “Spirsaure” which was already pure acetylsalicylic acid. It was also synthetised 1853 by Ch. Gerhardt and finally 1897 in Bayer´s laboratories by Felix Hoffmann, who also demonstrated its anti-inflammatory efficacy(Jerie, 2006).

The prototypes of antiphlogistic analgesics include acetylsalicylic acid (aspirin), acetanilide (the forerunner of acetaminophen), and phenazone. Advances in the knowledge of chemical structure of drugs in 19^{th}-20^{th} century along with the attempts to improve the effects and reduce the side effects of analgesics-antipyretics led to the development of other aspirin-like drugs called non-steroidal anti-inflammatory drugs (Brune & Niederweis, 2007).

Most of the NSAIDs were initially organic acids, but later non-acidic compounds were discovered. The drug discovery of NSAIDs can be divided in to two periods the time span from the post-World War 2 till the 1970´s was the pre-prostaglandin period and thereafter up to the later part of the last century was the period in which the effects on the production of prostaglandin were considered during the drug-discovery process (Rainsford, 2007).

In 1946, the Institute for the Study of Analgesic and Sedative Drugs awarded a grant to the New York City Department of Health to study the problems associated with analgesic agents. Bernard Brodie and Julius Axelrod were

assigned to investigate why non-aspirin agents were associated with the development of methemoglobinemia, a condition that decreases the oxygen-carrying capacity of blood and is potentially lethal. In 1948, Brodie and Axelrod linked the use of acetanilide with methemoglobinemia and determined that the analgesic effect of acetanilide was due to its active metabolite paracetamol. They advocated the use of paracetamol, since it did not have the toxic effects of acetanilide (Brodie & Axelrod, 1948).

1.3 Chemical Structure

Paracetamol is virtually the sole survivor of the so-called “aniline derivatives” or “aniline analgesics”. These aniline derivatives include acetanilide, phenacetin and paracetamol (acetaminophen). Phenacetin and paracetamol are both derivatives of acetanilide (Bertolini *et al.*, 2006) (Fig.1).

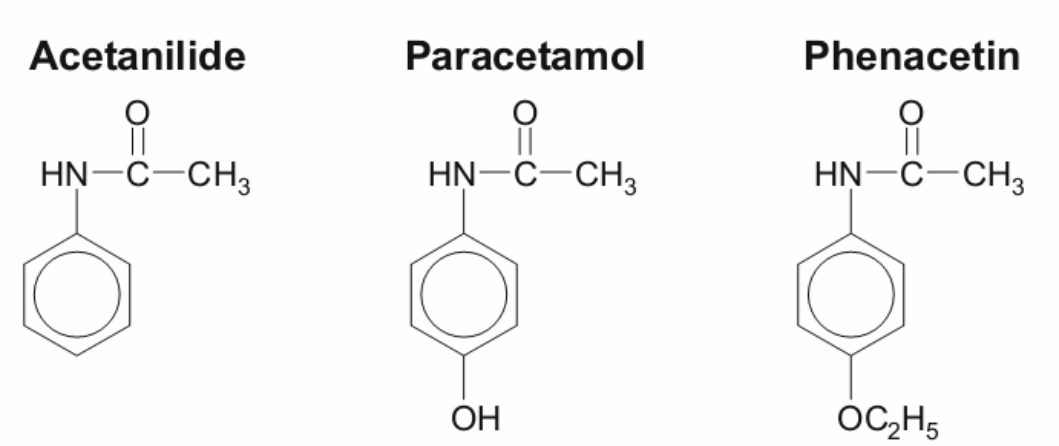


Fig.1 Chemical structures of “aniline” analgesics

Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para pattern (Mutschler, 1991). The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p-orbital on the carbonyl carbon and the lone pair on the carbonyl oxygen are all conjugated. The presence of two activating groups also makes the benzene ring highly reactive towards electorphilic aromatic substitution. As the substituents are ortho, para

directing and para with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygen and the nitrogen, while making the hydroxyl acidic through delocalisation of charge developed on the phenoxide anion.

1.4 Indications and applications

In view of its proven efficacy and low toxicity paracetamol is used on a worldwide basis. The analgesic and antipyretic effects of paracetamol are accepted to be of therapeutic significance, while its anti-inflammatory and anti-rheumatic activities are negligible (Clissold, 1986).
The spectrum of indications includes from the discomforts of the common cold over the post operative pain to the pain associated with malignancy. The analgesic efficacy of paracetamol is equivalent to that of aspirin, and its plasma levels required for the analgesic activity are higher than those needed for the antipyretic activity (Beck *et al.*, 2000).
As an analgesic and antipyretic paracetamol replaces aspirin especially in cases where aspirin is contraindicated. It has a broad tolerability and is of particular value in the treatment of patients in whom non-steroidal-anti-inflammatory drugs (Graham *et al.*, 1999) are contraindicated such as aspirin-sensitive asthmatics and people at risk of gastrointestinal complications (Prescott, 2000).
Paracetamol is available in oral, rectal and intravenous applicable forms. Oral administration of paracetamol as part of multimodal pain management immediately post-operatively resulted in a huge and unpredictable variation in plasma concentration compared with the intravenous administration (Holmer *et al.*, 2004). Intravenous administration of paracetamol either as intravenous acetaminophen or Propacetamol avoids variability associated with gastric absorption and first-pass hepatic metabolism, resulting in higher plasma concentrations and greater analgesic efficacy than orally administered drug (Jarde O & Boccard E, 1997).

Propacetamol (Pro-Dafalgan® or Pro-Efferalgan®), inject able prodrug of paracetamol, is in many European countries the first inject able paracetamol-

formula brought in the market. Perfalgan® is a newly developed intravenous applicable paracetamol of second generation.

In reference to anaesthesiological pain management in peri-operative (Kehlet & Dahl, 1993) as well as in special (adjunctive) pain treatment, paracetamol is indicated as follows:

- Treatment of moderate pain especially as an additive to other measurements.
- As an opioid sparing drug to reduce the side effects associated with opioid analgesics (e.g. respiratory depression).
- Treatment of fever for adults and children over 10 kg body weight.

Apart from that the drug is indicated by patients with known pseudo allergy against Metamizol by patients with blood disorders (agranulocytosis by Metamizol), especially by children(Hedenmalm & Spigset, 2002).
Lastly the i.v. analgesics like Prerfalgan® cover the gap created by the removal of COX2-inhibitors from the market.

1.5 Side effects

Paracetamol is a safe drug at appropriate dosage with a therapeutic index of approximately 10. The therapeutic dosage of paracetamol is 10-15mg/kg, and a dose of 7.5g in an adult or 150 mg/kg in a child are considered as the lowest acute dose capable of causing toxicity.
The very low level of paracetamol binding to plasma proteins, together with its hepatic metabolism, mainly through glucuronide or sulphate conjugation, account for the low risk of drug interactions with paracetamol, particularly with antivitamin K. When added to a traditional NSAID, paracetamol enhances the analgesic effect or allows the use of lower doses (Bannwarth & Pehourcq, 2003).

The safety of paracetamol was reported in patients with stable chronic liver disease showing no evidence of accumulation or hepatotoxicity after the administration of the drug in therapeutic doses (Benson, 1983).

A clinical significant damage of liver cells is rare after therapeutic doses of paracetamol however; the incidence of acute liver failure is reported even after therapeutic doses (Pearce & Grant, 2008).

The side effects of paracetamol are usually associated with its overdoses but rare incidence of anaphalctoid reaction after therapeutic doses of paracetamol is also reported (Ayonrinde & Saker, 2000)

Acute renal failure is not uncommon in paracetamol poisoning and appears to be unrelated to the degree of liver injury (Mour *et al.*, 2005). However, there are many conditions which might play a role as influencing factor in causing renal complications after paracetamol overdoses; they include concomitant ingestion of nephrotoxic drugs, dehydration, chronic excessive dosing (von Mach *et al.*, 2005) of acetaminophen, pre-existing renal or liver disease and multiple organ failure (von Mach *et al.*, 2005).

1.6 Mechanism of action

The mechanism of action of paracetamol analgesia is not fully understood but involves multiple factors. It is a potent inhibitor of prostaglandin synthesis within the central nervous system (Piletta *et al.*, 1991).
The prostaglandins are lipid mediators. The formation of prostaglandins is catalysed by the enzyme cyclooxygenase (COX). COX is a bifunctional enzyme having both cyclooxygenase and peroxydase activities. Prostaglandins are involved in physiological functions of the body such as protection of the stomach mucosa, aggregation of platelets and regulation of kidney functions however; they also have pathological functions and involve in the processes of inflammation, pain and fever. In 1971, Sir John Vane demonstrated for the first time that the mechanism of action of aspirin and other non-steroidal anti-inflammatory drugs (Graham *et al.*, 1999) is via inhibition of COX. A second cyclooxygenase (Brune & Neubert, 2001) was identified in 1991 by Simmon and his colleagues. The inflammatory mediators upregulate COX-2, increasing prostaglandin formation that intensify the inflammatory response(Botting, 2006). A third variant of COX

designated by some authors as COX-3 has been reported. This enzyme is produced by cyclooxygenase-1 gene, but retains intron 1 after transcription and translates into a cyclooxygenase enzyme with 34 additional amino acids. It is experimented in specific tissues and shows a high concentration in brain and heart. It is selectively inhibited by analgesic/antipyretic agents like paracetamol and NSAIDs, however not through COX-2-selective inhibitors. This enzyme is possibly a central mechanism for the analgesic/antipyretic effects of paracetamol (Chandrasekharan *et al.*, 2002).

The results obtained from paracetamol could not show systemically an effective inhibition of peripheral COX. A few positive results were obtained from in vitro tests (COX-1/COX-2-inhibition) on intact cells or human full blood. However as opposed to this finding, in vivo tests the peripheral COX-2-inhibition through paracetamol should be very limited. This difference of in-vivo- and in-vitro-effects can be due to the higher concentration of peroxides in inflamed tissue (Ouellet & Percival, 2001).

Some reports suggest the modulation of the serotoninergic system as a possible mechanism of paracetamol antinociceptive activity and indicate that the drug may stimulate the activity of descending 5-HT pathways that inhibit the nociceptive signal transmission in the spinal cord (Bonnefont *et al.*, 2003). Other studies suggest a supraspinal target for acetaminophen's antinociceptive action and a central serotonergic mechanism of action for acetaminophen that is not stimulus-dependent (Pickering *et al.*, 2007).
The central mechanism of action of paracetamol is supported by the observations that paracetamol crosses the blood-brain barrier rapidly leading to a high concentration of the drug in cerebrospinal fluid (CSF) and a parallel time-course of paracetamol concentration in CSF and its analgesic effect (Bannwarth *et al.*, 1992)

Paracetamol also acts peripherally by blocking impulse generation within the bradykinin-sensitive chemo receptors responsible for the generation of nociceptive impulses.

Paracetamol is thought to have an analgesic effect by antagonising NMDA and substance P in the spinal cord. Analgesic effect also involves an inhibitory action on spinal nitric oxide mechanisms (Clissold, 1986; Piletta *et al.*, 1991; Bjorkman, 1995).

It is also reported that the analgesic effects of paracetamol involve the indirect activation of cannabinoid (CB) receptors; and in the central nervous system (CNS) paracetamol after its deacetylation to its primary amine (p-aminophenol), conjugate with arachidonic acid to form N-arachidonoylphenolamine. N-arachidonoylphenolamine is known to act as an endogenous CB. Thus paracetamol act as a pro-drug and the active form being the CB (Hogestatt *et al.*, 2005; Bertolini *et al.*, 2006).

1.7 Pharmacokinetics

Paracetamol is rapidly absorbed after oral administration; peak plasma concentrations are reached in 30-60 minutes. The plasma half life of paracetamol with therapeutic doses is 2-4 hours but with toxic doses it may be extended to 4-8 hours. Paracetamol is rather evenly distributed in most of the body fluids. It is weakly bounded to the plasma proteins, and even in toxic doses only 20% - 50% of the substance is in a bounded form. By therapeutic doses, 90% -100% of the substance is found in the urine on first day of administration. Paracetamol is inactivated in liver, being conjugated to glucuronic acid (60%), sulphuric acid (35%) and cystines (3%). Minute quantities of hydroxylated and desacylated metabolites can also be detected. A small part of paracetamol is by cytochrom-450-dependant N-hydroxylation metabolised, that leads to the formation of N-acytylbenzochinonimin, a very reactive intermediate metabolite. This metabolite reacts normally with sulphydryl groups of glutathione, however after high doses of paracetamol, the glutathione stores of liver are used up. Under these conditions N-acytlybenzochinonimin reacts with the sulphydryl groups of liver proteins in such an extent that liver necrosis can develop (Paul A.Insel, 1940).

Studies have shown oral paracetamol to be very effective and good tolerable for post operative pain management (Weil *et al.*, 2007). However the use of paracetamol is limited to the treatment of mild to moderate pain or as a second-line-therapy many days after the operation. At an oral dose of 1000mg paracetamol reaches its ceiling effect in adults. No increase in analgesic activity occurs by further increasing the doses (Woodbury DM., 1965), but it does increase the toxicity.
After oral doses the absorption of paracetamol is not uniform but after an i.v. administration the plasma concentration is predictable.

After an infusion of paracetamol the maximum plasma concentration is much higher than that after oral doses, so that more of the substance can cross the blood-brain barrier. It can also explain the lack of Ceiling-Effect(Skoglund & Pettersen, 1991) after intravenous application of up to 2g of paracetamol. Intravenous acetaminophen exerted a dose-dependent central antinociceptive effect (Piguet *et al.*, 1998).

1.8 Current literature

The pharmacologic effects of paracetamol are not directly related to the concentration of the drug in plasma but they are related rather to an effect compartment. The concentrations of the effect compartment equate approximately to cerebrospinal fluid (CSF) (Anderson & Gibb, 2007a). The time and CSF concentration of paracetamol show a correlation with its antipyretic effect (Kozer *et al.*, 2007).
Paracetamol permeates readily into the CSF of children. This enables the rapid central analgesic and antipyretic action of intravenous paracetamol (Kumpulainen *et al.*, 2007).
Intravenous paracetamol crosses the blood-brain barrier rapidly and the elimination half-life of paracetamol was shorter in plasma than in CSF. Antipyretic and probably analgesic effects of Paracetamol are at least in part centrally mediated. The time-course of paracetamol in CSF may parallel that of analgesic effect (Bannwarth *et al.*, 1992).

Gregoire (Gregoire *et al.*, 2007) showed that after repeated doses of paracetamol with a maximum dose of 4g/day, the plasma concentrations remained under the toxic range, indicating the absence of accumulation.
In a study performed on children from neonates to adolescents to determine the age related changes in plasma and CSF equilibration half-time (Teq) of paracetamol showed that size rather than blood-brain-barrier maturation determines Teq changes with age in children (van der Marel *et al.*, 2003).

1.9 Aim of the trial

The aim of the trial was to evaluate, whether similar or comparable efficacious CSF levels of Perfalgan® could be obtained after an infusion of 1g over 60 minutes as compared to an infusion of 1g over 15 minutes in a porcine model.

2. Methods

2.1 Animals

This experimental procedure was performed on 10 female German domestic pigs. The approval of the experimental procedure was obtained from the local Animal Investigation Committee (Regierungspräsidium, Gießen) before starting the trial. The pigs were kept for one week under a phase of observation and familiarization, before the start of the experiment, in the animal experimental lab of the Philipps-University-Marburg.
The pigs were randomized by a computerized random-number generator either in the group which received the Perfalgan® infusion in 15 minutes or in the group receiving the Perfalgan® infusion in 60 minutes.

2.2 Pre medication and anaesthesia

The pre medication was done with an intramuscular application of diazepam 1mg/kg, ketamin 20mg/kg and atropine 0.2mg/kg bodyweight.
An intravenous line was taken in one of the dorsal ear veins with a 20 gauge canula. The induction of anaesthesia was performed with an intravenous injection of disoprivan 2mg/kg and fentanil 0.5µg/kg bodyweight as repetitive bolus, followed by tracheal intubation. The animals were ventilated with a Dräger anaesthesia machine (Sulla 808 V) and an intermittent positive pressure ventilation mode with a mixture of oxygen in air at an inspiratory concentration (FiO2) of 50% was used. The anaesthesia was maintained with a continuous infusion of Disoprivan (Propofol®) 1% at a rate of 10mg/kg/h and sufentanil 1µg/kg/h. No muscle relaxant was used.

2.3 Infusion protocol

The pigs were randomized in two groups. Group one (n=5) received an infusion of 1g Perfalgan over 15 minutes. In this group (15-min-group), plasma and CSF samples were taken at 15, 30, 60, 90, 120, 150, 180, and 210 minutes after starting the infusion.

Group two (n=5) received an infusion of one gram of Perfalgan over 60 minutes. In this group (60-min-group), the first plasma sample was taken 60 minutes after starting the infusion and repeated after every 30 minutes up to 210 minutes. The CSF samples in this group (60-min-group) were obtained at 90, 120, 150, 180, and 210 minutes after starting the infusion.

Plasma samples were taken through a central venous catheter. In order to obtain the CSF, we performed a lumber puncture at the levels of second, third or fourth lumber vertebra with a 25 gauge spinal needle (Quincke needle 25G) and kept the needle in place.
The samples were collected into tubes with no additives and transported to the central laboratory of the University Hospital Marburg immediately after the procedure.

2.4 Laboratory Methods

The laboratory measurement of paracetamol was performed with Synchron® **-** System(s) (Beckman Coulter, Inc.) with the help of acetaminophen (ACTM) reagent. ACTM reagent is used to measure ACTM concentration by a particle enhanced turbidimetric inhibition immunoassay method (Newman *et al.*, 1992). A Particle-bound drug (PBD) binds to the analyte specific antibody (Ab) resulting in the formation of insoluble aggregates causing light scatter. Non particle-bound analyte in the patient sample competes with the PBD for the antibody binding sites, inhibiting the formation of insoluble aggregates. The System monitors the aggregate formation by measuring the change in the absorbance at 340 nanometers. This change in absorbance is inversely proportional to the concentration of ACTM based on a multi-point calibration curve. The same methods were applied for the measurements of paracetamol concentrations in plasma and CSF.

The chemical reaction can be shown by the following equation.

Acetaminophen (sample)+PBD+Ab → PBD–Ab(aggregates)+Acetaminophen(sample)- Ab

2.4.1 Analytic range

The method for the determination of this analyte provides the following analytic range.

Table1.

Sample Type	Conventional Units	S.I. Units
Serum or Plasma	10 – 300 µg/mL	66 – 1986 µmol/L

Legends: S.I.: Standard International; mL: milliliters; µg: microgram; µmol/L: micromole per liter

2.4.2 Sensitivity

Sensitivity is defined as the lowest measurable concentration which can be distinguished from zero with 95% confidence.
Sensitivity for ACTM determination is 2.5 µg/mL (16 µmol/L).

2.4.3 Specificity

Most of the substances added at the concentrations from 50 µg/mL to 1000 µg/mL to separate aliquots of a serum pool containing 40 µg/mL acetaminophen produced no significant interference (within ± 8%).

2.5 Pharmacokinetics

A compartmental analysis of the pharmacokinetic estimates was performed using the software packet TopFit (Thomae Optimized Pharmacokinetic Fitting Program), Version 2.0 (Heinzel G. *et al.*, 1993).

2.5.1 Pharmacokinetic model

A two compartment model with first-order elimination and i.v. bolus dosing was used where plasma is the central compartment and brain is the peripheral compartment. The two compartment model fits better and is in accordance with the literature; moreover a three compartment model did not fit to the data.

2.5.2 Weighting and goodness-of-fit

The goodness-of-fit was evaluated by visual inspection of predicted vs. observed data and from plots of residuals. The individual weighting was performed for each measured value by the use of the mathematical algorithm from TopFit.

2.5.3 Measured parameters

Elimination half-life (t 1/2 beta), total clearance (Cl(t)), mean resident time (MRT), area under the curve (AUC) and volume of distribution at equilibrium (Vd(ss)) were calculated.
The significance of the values was calculated by using the Mann-Whitney U test.

3. Results

3.1 Age, gender and body weights

This experiment was performed on female pigs. The age of the animals in both groups were on an average about twelve weeks, with no relevant difference between the groups. The bodyweights of the animals in both of the groups were also comparable. The age and bodyweights of the subjects are shown in the following table below.

Table 2. Age and weight of animals.

Group	Age of the animals	Weight of the animals
15-min	11 – 13 weeks	38.8 kg – 41.7 kg
60-min	11 – 14 weeks	38.5 kg – 41.9 kg

Legends: kg: kilogram; min: minutes.

3.3 Plasma Levels of paracetamol

The plasma levels of paracetamol were measured in individual animals at regular intervals.

3.3.1 Individual Plasma Levels in 15-min-group

The values of plasma concentration of Paracetamol obtained from individual animals in 15-min-group are shown in table 3.

Table3. Individual levels of Paracetamol observed in 15-min-group.

Animal No.	**Plasma Levels [mg/l] 15-min-group**							
	15min	30min	60min	90min	120min	150min	180min	210min
1.	32.5	16.0	10.4	10.0				
2.	28.7	24.7	22.6	18.7	14.0	14.5	11.8	
3.	33.1	27.8	23.2	18.1	16.5	13.0	117	
4.	77.3	32.4	24.5	20.2	17.2	14.6		
5.	40.0	34.6	33.5	27.2	25.3	21.4	19.8	

Legends: min: minutes; mg/l: milligram per liter; No.: Number.

3.3.2 Individual Plasma Levels in 60-min-group.

The plasma levels of paracetamol in individual subjects in the 60-min-group are listed in table 4.

Table 4. Individual plasma levels of paracetamol in 60-min-group.

Animal No.	**Plasma Levels [mg/l] 60-min-group**							
	15min	30min	60min	90min	120min	150min	180min	210min
6.	24.2	29.4	28.5	21.0	17.9	18.1	14.4	
7.		20.1	37.3	22.8	30.6	28.6	25.3	23.3
8.			33.4	37.1	27.0	23.2	20.2	19.2
9.		18.7	24.2	17.2	24.2	20.8	19.2	17.8
10.	12.8	33.0	48.7	39.4	32.9	27.1	23.5	

Legends: min: minutes; mg/l: milligram per liter; No.: Number.

3.3.3 Mean Plasma Levels

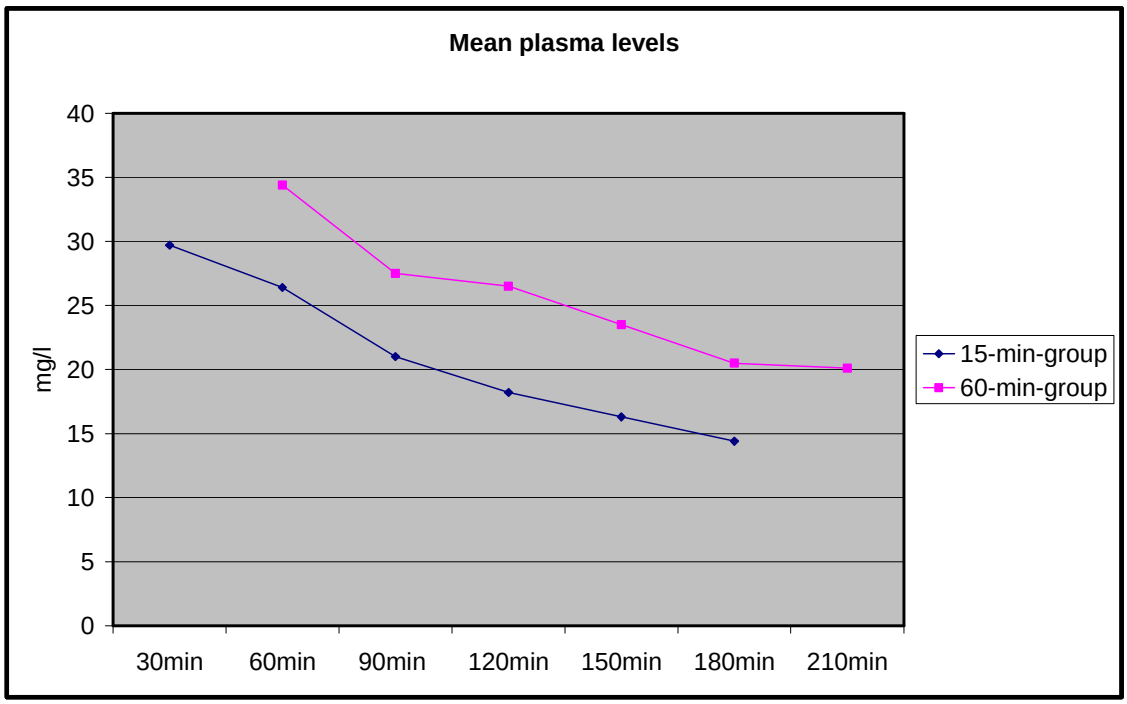
The mean plasma levels were higher in 60-min-group as compared to those in the 15-min-group. The obtained data is listed in the table 5.

Table 5. Mean plasma levels in both groups.

Group	Mean plasma levels [mg/l] (Standard Deviation)							
	15min	30min	60min	90min	120min	150min	180min	210min
15min	40.6 (21.2)	29.7 (3.8)	26.4 (4.5)	21 (3.6)	18.2 (4.2)	16.3 (3.4)	14.4 (3.8)	
60min			34.4 (8.3)	27.5 (9.0)	26.5 (5.2)	23.5 (3.8)	20.5 (3.7)	20.1 (2.3)

Legends: min: minutes; mg/l: milligram per liter; No.: Number.

The comparison between the plasma levels of paracetamol in plasma is shown in Fig. 2.



Legends: min: minutes; mg/l: milligram per Liter.

Figure 2. Mean plasma levels in the groups.

3.4 CSF Level of paracetamol

The concentrations of paracetamol measured at regular interval in both groups of animals are given in the following tables.

3.4.1. Individual CSF Levels in 15-min-group

The individual levels of paracetamol concentration measured in CSF of 15-min-group are given in table 6.

Table 6. CSF levels of Paracetamol in 15-min-group.

Animal No.	**CSF Levels [mg/l] 15-min-group**							
	15min	30min	60min	90min	120min	150min	180min	210min
1.								
2.		13.3	16.0	14.0	12.7	15.4	14.7	13.6
3.	10.7	11.8	12.8	14.7	13.8	12.5	12.6	
4.				10.1	12.0	12.3		
5.			11.0	13.7	16.3	17.0	16.1	

Legends: CSF: Cerebrospinal fluid; min: minutes; mg/l: milligram per Liter; No.: Number.

3.4.2. Individual CSF Levels in 60-min-group.

The data obtained from individual levels of CSF concentrations of paracetamol in 60-min-group is listed in table 7.

Table 7. CSF levels of Paracetamol in 60-min-group.

Animal No.	**CSF Levels [mg/l] 60-min-group**							
	15min	30min	60min	90min	120min	150min	180min	210min
6.			13.3	16.1	14.8	16.9	20.0	
7.					12.5	18.5	20.2	20.5
8.				12.6	12.2	19.8	21.0	18.1
9.					10.0	11.6	13.5	13.0
10.				10.8	17.7	18.3	19.3	

Legends: CSF: Cerebrospinal fluid; min: minutes; mg/l: milligram per Liter; No.: Number.

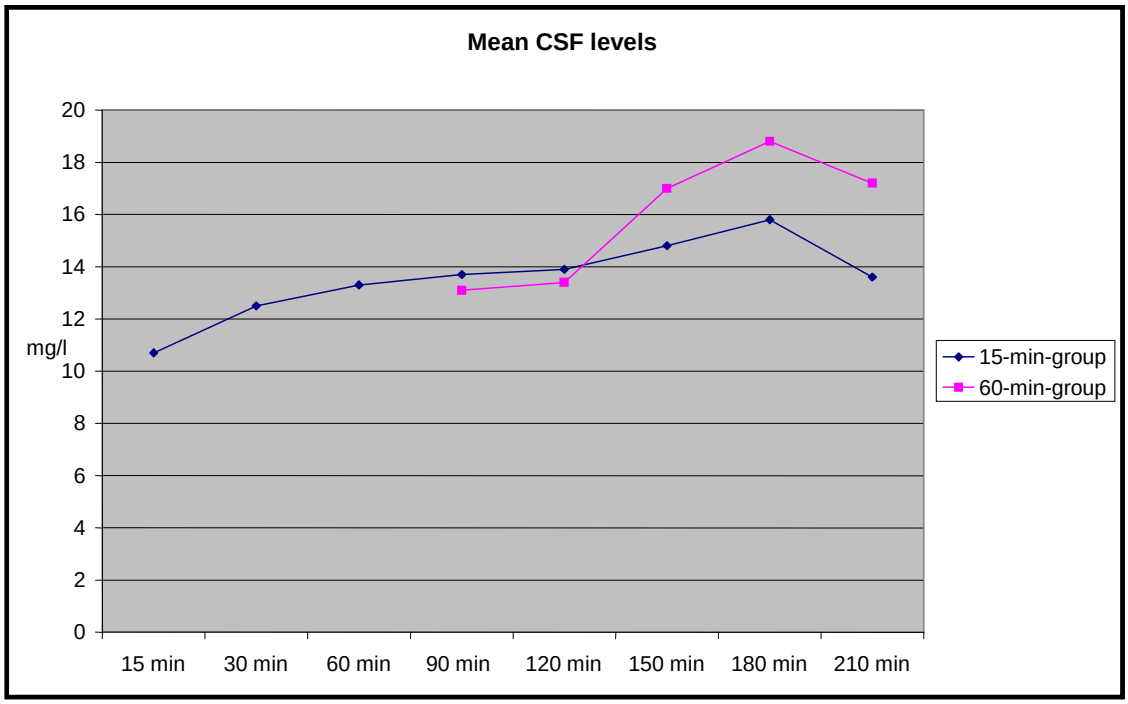
3.4.3 Mean CSF Levels

In the time interval between 150 and 210 minutes CSF levels were higher in both groups. The results of plasma and CSF levels are shown in tables 8 and figures 3.

Table 8. Mean CSF levels in both groups.

Group	**Mean CFS [mg/l] (Standard Deviation)**							
	15 min	30 min	60 min	90 min	120 min	150 min	180 min	210 min
15-min	10.7 (1.2)	12.5 (1.1)	13.3 (2.1)	13.7 (2.2)	13.9 (1.7)	14.8 (2.3)	15.8 (3.1)	13.6 (3.1)
60-min				13.1 (2.2)	13.4 (2.5)	17.0 (2.8)	18.8 (2.7)	17.2 (3.1)

Legends: CSF: Cerebrospinal fluid; min: minutes; mg/l: milligram per Liter.



Legends: CSF: Cerebrospinal Fluid; mg/l: milligram per Liter.

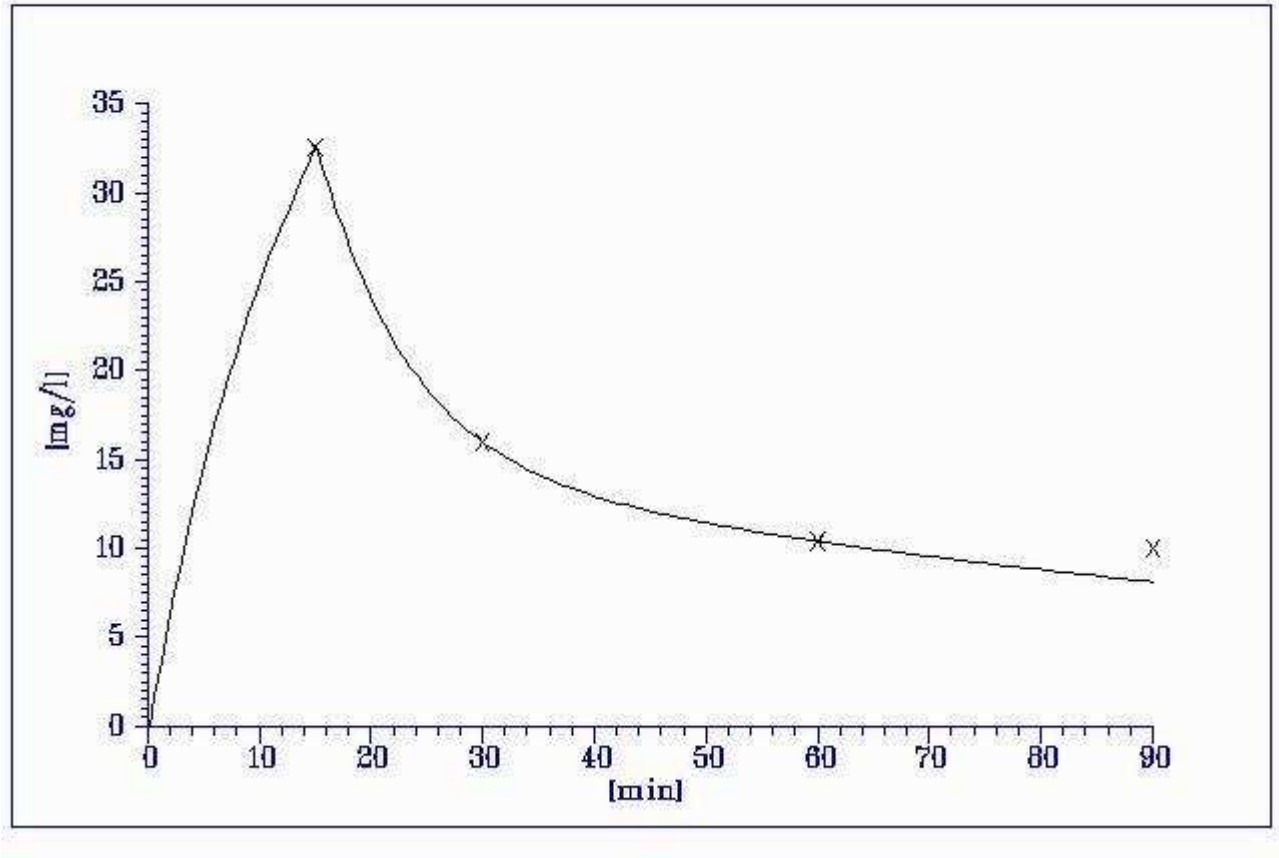
Figure 3. Mean CSF level measured in both groups.

3.5 Pharmacokinetics

The pigs in both groups showed the comparable maximum plasma concentration C(Max). The C(Max) values for both the groups were as follows: 15-min-group (median+/-SD) 35.1±17.48 and 60-min-group (median±SD) 37±7.42 mg/l. The elimination half-lives (t ½ beta) were (median±SD) 120± 28.72 min. in the 15-min-group and 176± 127.62min in the 60-min-group. For t ½ beta the difference between the two groups was statistically significant (Mann-Whitney-U, P=0.03). The clearance (Cl) was higher in the 15-min-group (median±SD) 181±67 ml/l as compared to that in the 60-min-group (median±SD) 94.9±45.73 ml/l (P=0.01).

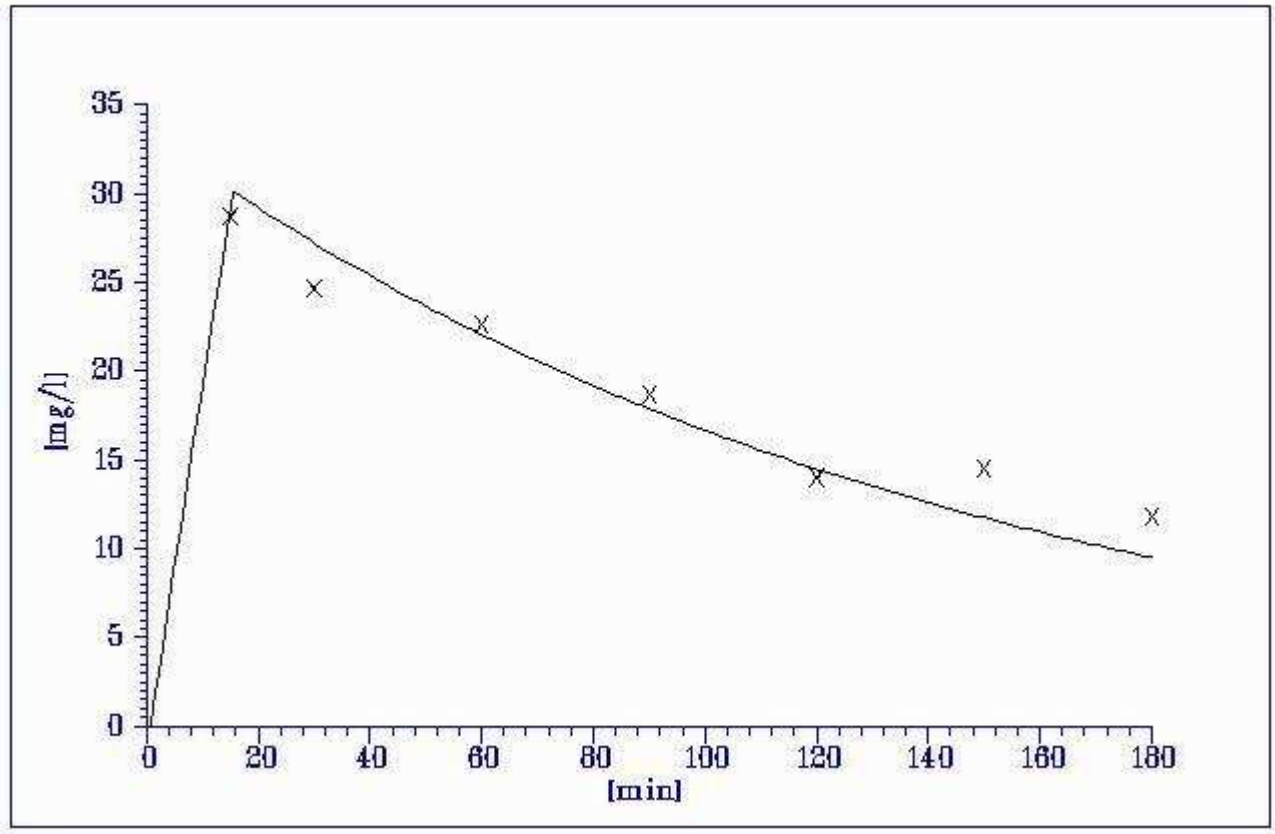
The median volumes of distribution at steady state (Vss) were comparable in both the groups; Vss was (median+/-SD) 31.5±8.46 l in 15-min-group and 25.2±8.18 l in the 60-min-group. The pigs in the 60-min-group showed a distinct prolongation of the elimination half-life of paracetamol compared to the pigs in the 15-min-group. Therefore the duration of i.v. infusion of paracetamol for the treatment of postoperative analgesia should be increased to achieve a prolonged pain free period in the postoperative phase.

The individual plasma concentrations of paracetamol measured in 15-min-group plotted against time are shown in the figures 4 to 8.



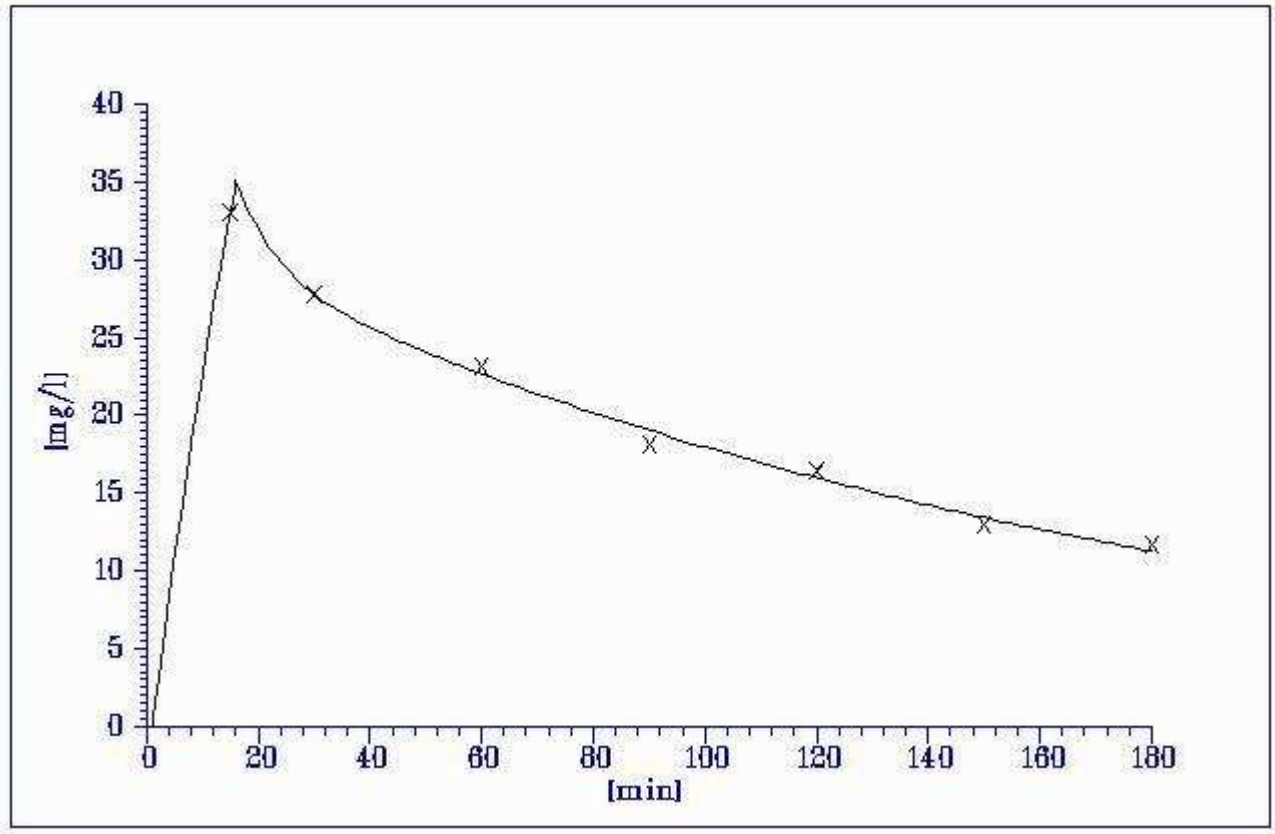
Legends: mg/l: milligram per Liter; min: minutes.

Figure 4. Plasma levels in animal No.1 (15-min-group).



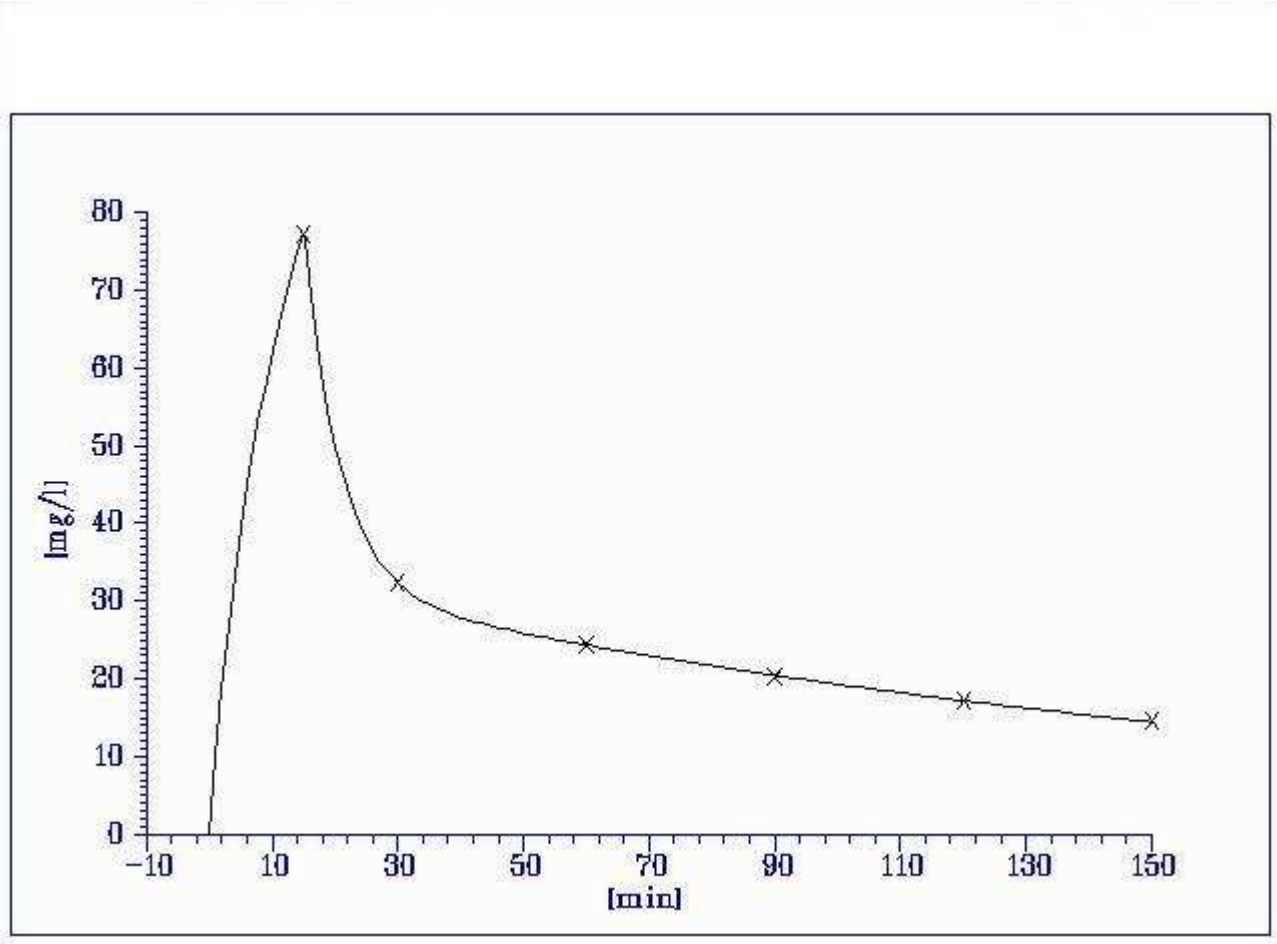
Legends: mg/l: milligram per Liter; min: minutes.

Figure 5. Plasma levels in animal No.2 (15-min-group).



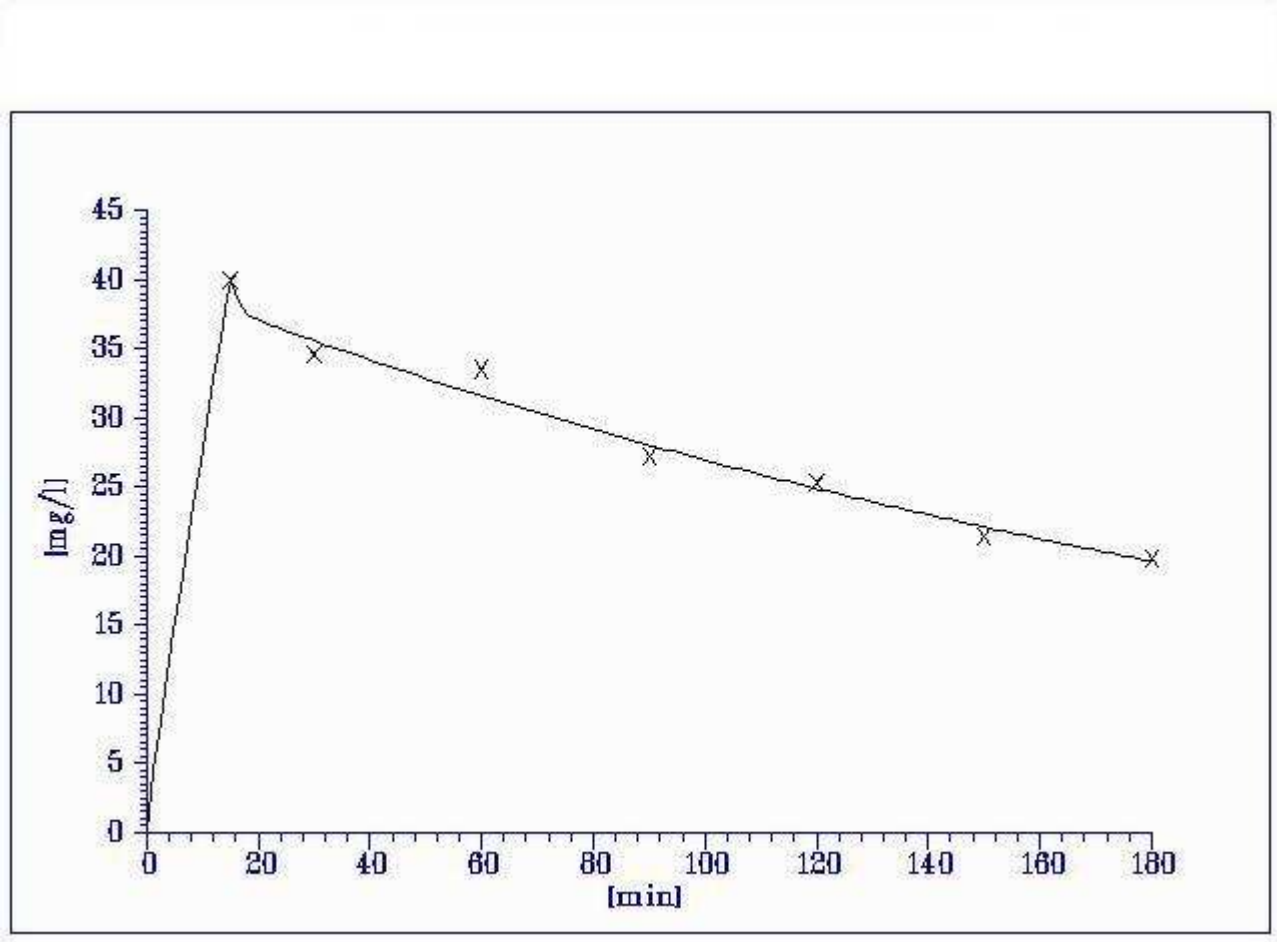
Legends: mg/l: milligram per Liter; min: minutes.

Figure 6. Plasma levels in animal No.3 (15-min-group).



Legends: mg/l: milligram per Liter; min: minutes.

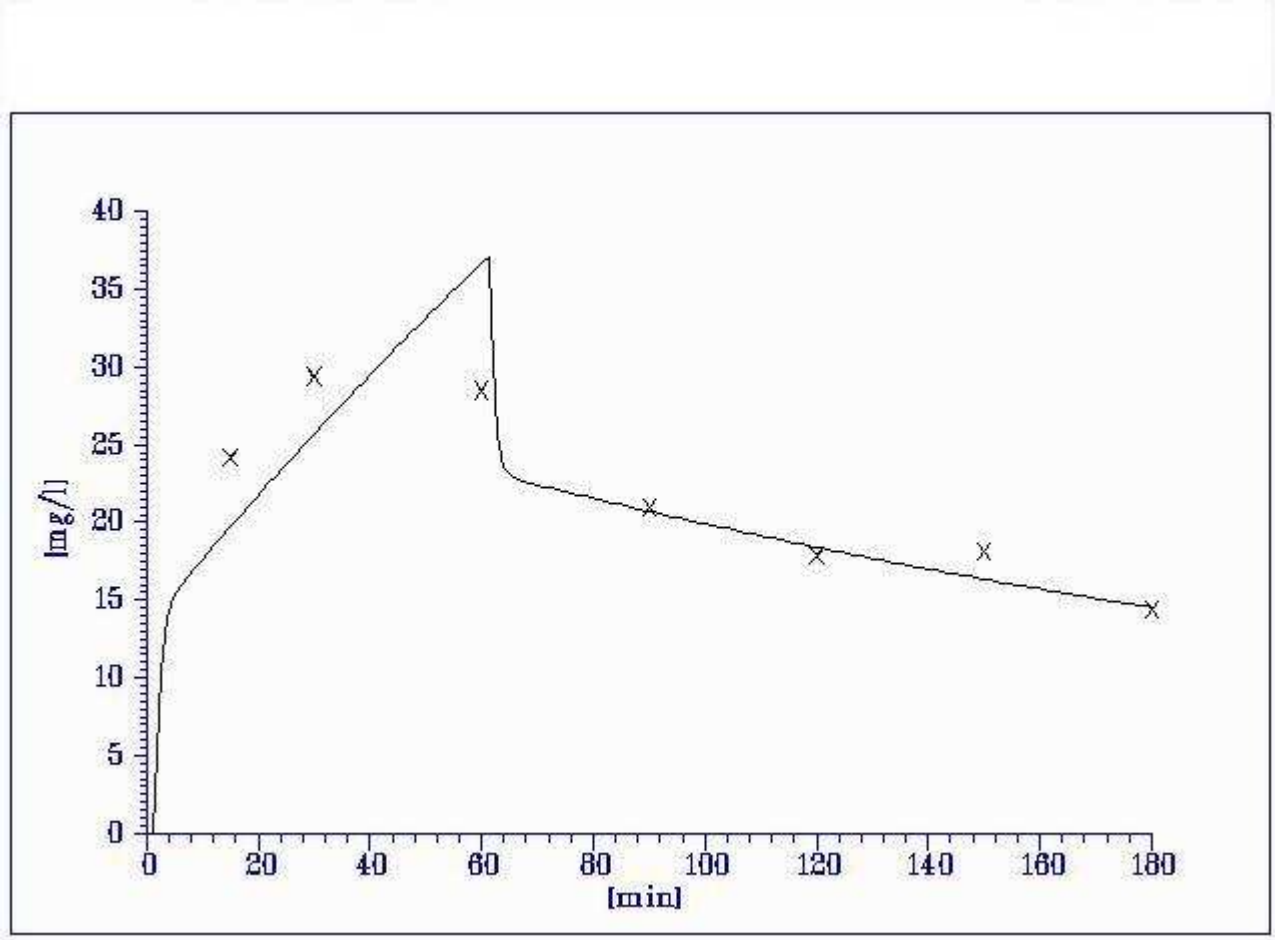
Figure 7. Plasma levels in animal No.4 (15-min-group).



Legends: mg/l: milligram per Liter; min: minutes.

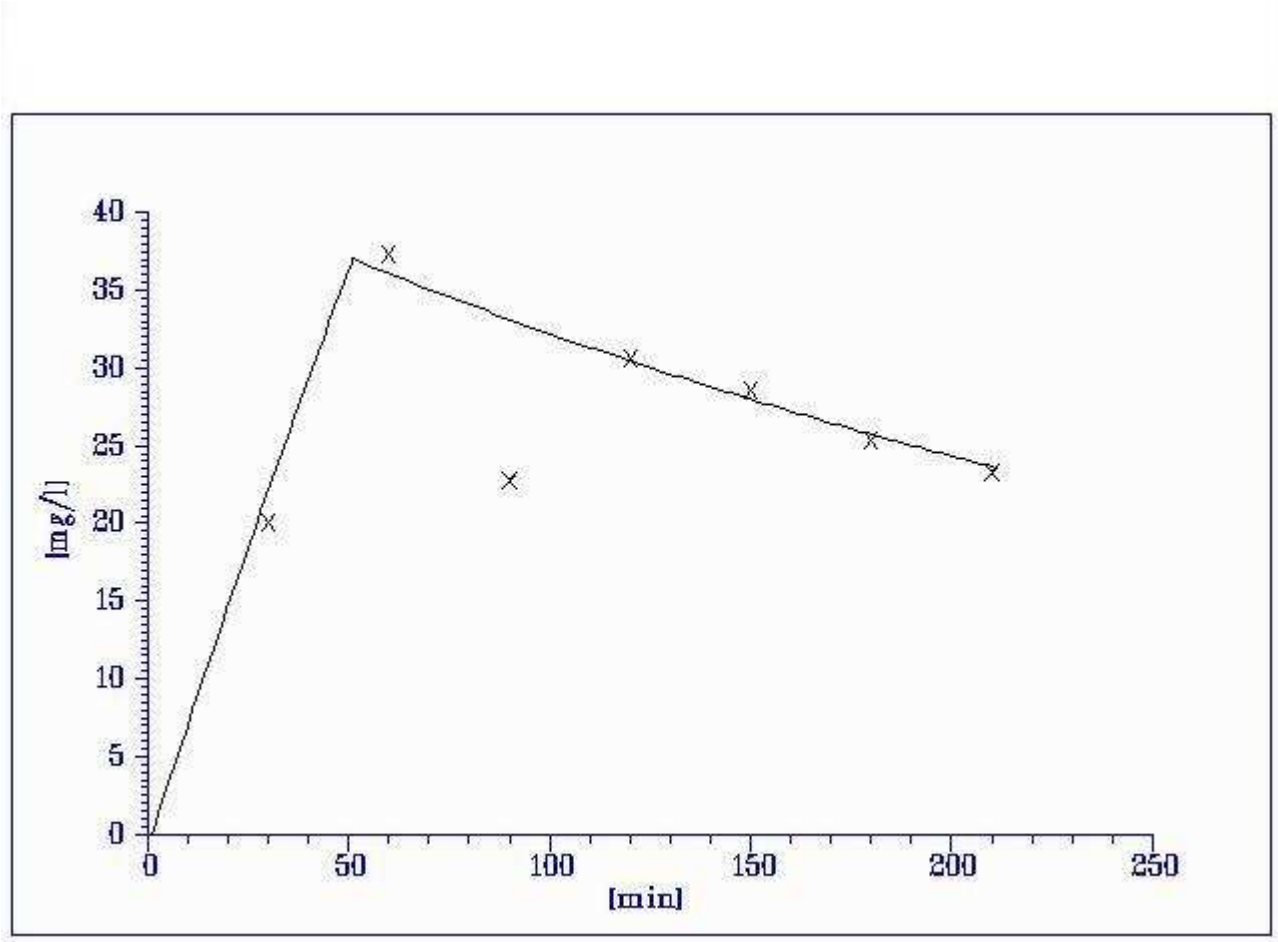
Figure 8. Plasma levels in animal No.5 (15-min-group).

The figures 9 to 13 show the individual plasma concentrations of paracetamol plotted against time measured in 60-min-group.



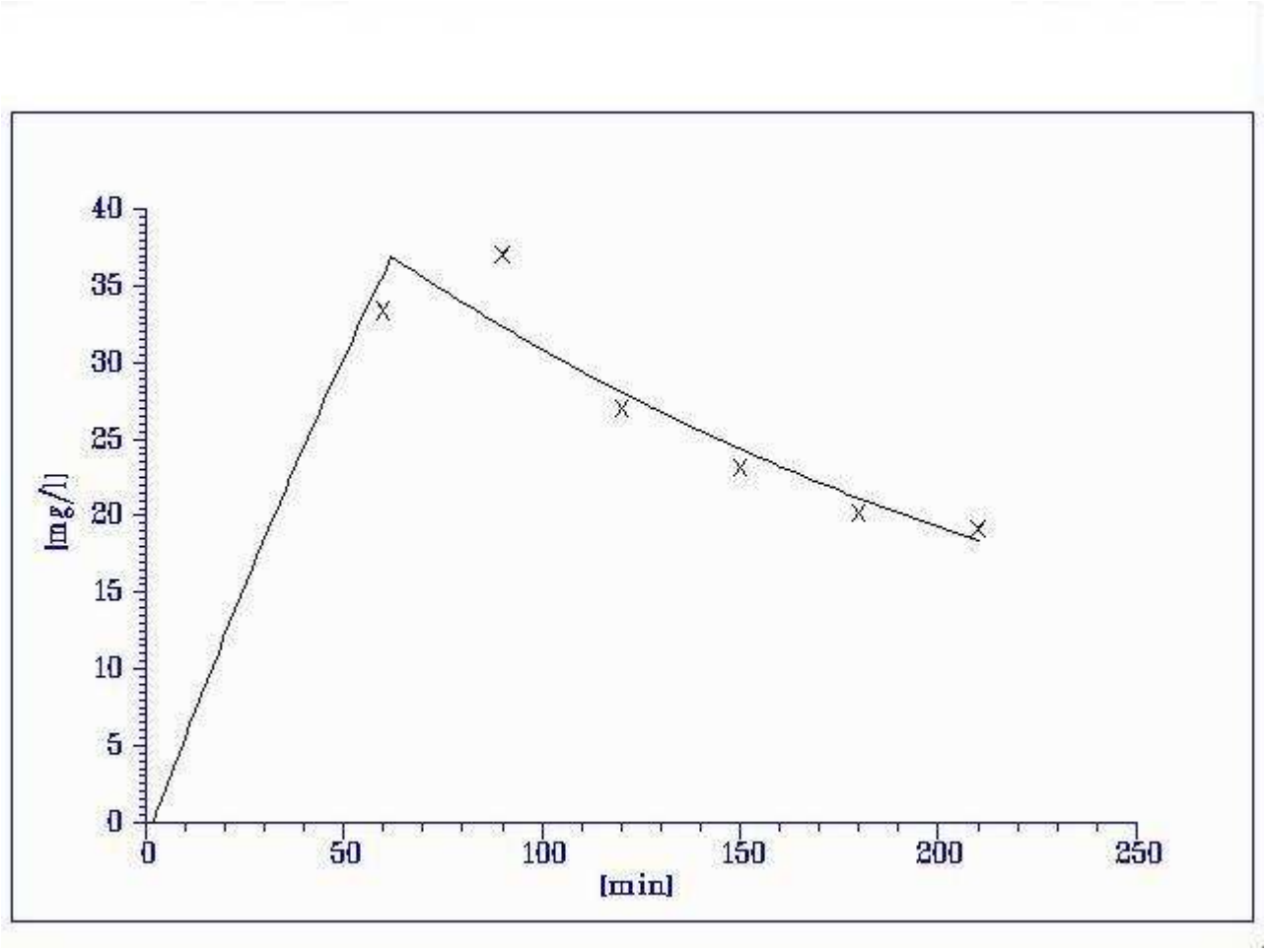
Legends: mg/l: milligram per Liter; min: minutes.

Figure 9. Plasma levels in animal No.6 (60-min-group).



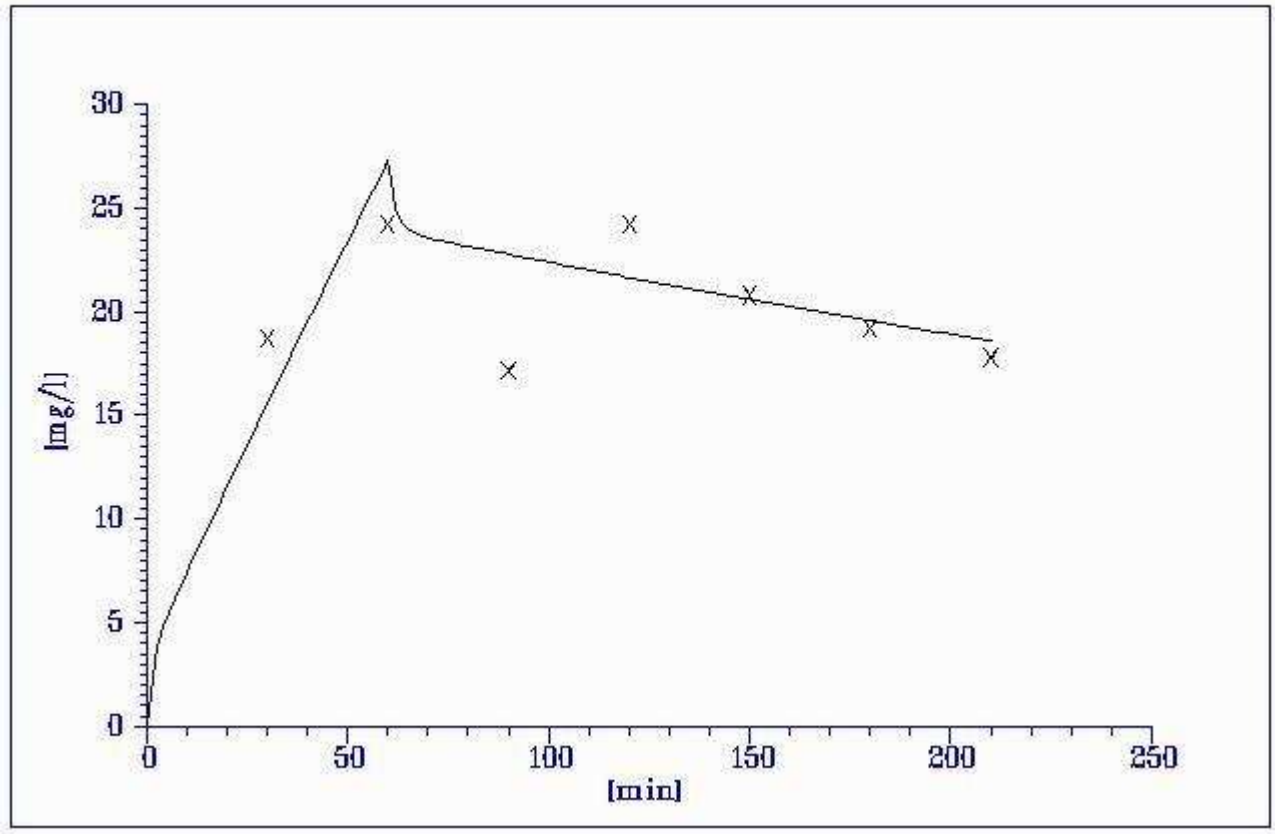
Legends: mg/l: milligram per Liter; min: minutes.

Figure 10. Plasma levels in animal No.7 (60-min-group).



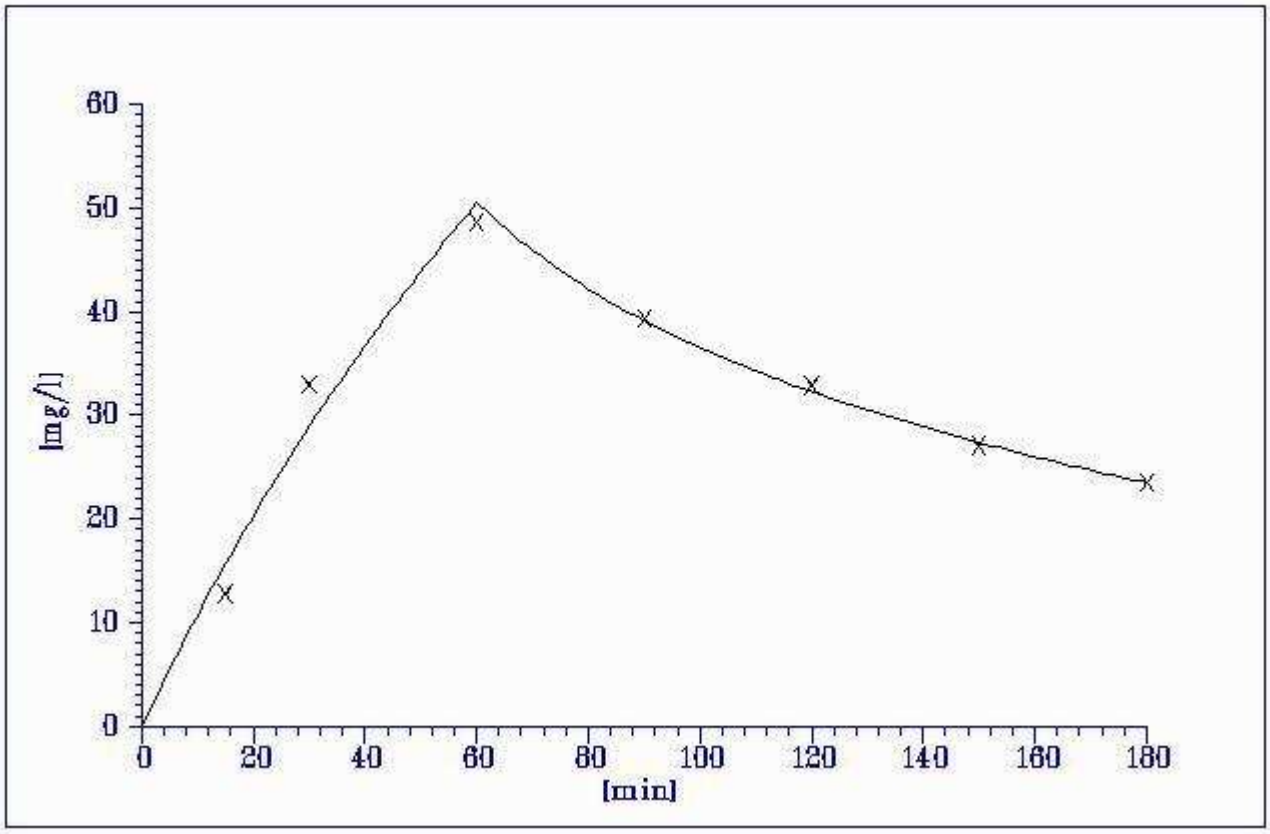
Legends: mg/l: milligram per Liter; min: minutes.

Figure 11. Plasma levels in animal No.8 (60-min-group).



Legends: mg/l: milligram per Liter; min: minutes.

Figure 12. Plasma levels in animal No.9 (60-min-group).



Legends: mg/l: milligram per Liter; min: minutes.

Figure 13. Plasma levels in animal No.10 (60-min-group).

The following tables show the values calculated from plasma concentrations of Paracetamol with the help of TopFit 2.0.
The Table 9 shows the individual pharmacokinetic values obtained from 15-min-group.

Table 9. Elimination half-life, Mean resident time total, Volume of distribution at steady state, Clearance, Area under the curve and Maximum plasma concentrations in 15-min-group.

Measured pharmacokinetic values in 15-min-group					
Animal No.	1	2	3	4	5
b2 t50% (min)	86.4	135	119	120	175
MRT-tot (min)	116	202	177	161	258
Vss (l)	47.6	35	31.5	23.9	25.5
Cl (ml/min)	439	181	187	155	102
AUC-model (mg/l*min)	2280	5530	5360	6450	9830
Cmax (mg/l)	32.7	29.8	35.1	77.3	40

Legends: AUC: Area under the curve; b2 t50%: Elimination half-life; Cl: Clearance; Cmax: Maximum plasma concentration; min: minutes; MRT-tot: Mean resident time total; No.: Number; Vss: Volume of distribution at steady state.

The individual pharmacokinetic values obtained from 60-min-group are given in table 10 below.

Table 10. Elimination half-, Mean resident time total (MRT-tot), Volume of distribution at steady state, Clearance, Area under the curve and Maximum plasma concentration in 60-min-group.

Measured pharmacokinetic values in 60-min-group					
Animal No.	6	7	8	9	10
b2 t50% (min)	176	247	130	411	143
MRT-tot (min)	256	383	244	615	226
Vss (l)	30.3	25.2	23.6	38.7	18.6
Cl (ml/min)	134	70.7	111	66.1	94.9
AUC-model (mg/l*min)	7440	14100	8980	15100	10500
Cmax (mg/l)	37.1	37	37	27.3	50.6

Legends: AUC: Area under the curve; b2 t50%: Elimination half-life; Cl: Clearance; Cmax: Maximum plasma concentration; min: minutes; MRT-tot: Mean resident time total; No.: Number; Vss: Volume of distribution at steady state.

Table 11. The comparison between different pharmacological values along with the significance measured using the Mann-Whitney test is listed in table below.

Comparison of calculated pharmacological values in both groups												
	b2 t50% (min)		MRT-tot (min)		Vss (l)		Cl (ml/min)		AUC (mg/l*min)		C(max) (mg/l)	
Groups	A	B	A	B	A	B	A	B	A	B	A	B
Mean	127.08	221.4	182.80	287.37	32.7	22.76	212.8	57.25	5890	11224	42.98	37.8
Median	120	176	177	256	31.5	8.18	181	94.9	5530	10500	35.1	37
SD	28.72	127.62	46.89		8.46	25.2	67.02	45.73	2420	2938	17.48	7.42
Sig.	0.03		0.03		0.1		0.01		0.01		0.5	

Legends: AUC: Area under the curve; b2 t50%: Elimination half-life; Cl: Clearance; Cmax: Maximum plasma concentration; min: minutes; MRT-tot: Mean resident time total; No.: Number; SD: Standard deviation; Sig.: Significance; Vss: Volume of distribution at steady state.

4. Discussion

4.1 Summary of the Results

We studied the pharmacokinetics of intravenous paracetamol using different infusion rates. One of the two groups (n=5) received 1g of paracetamol over 15 minutes and the other group (n=5) over 60 minutes.

The results show that in the time interval between 60 and 180 minutes after starting the infusion, the plasma levels of paracetamol were found to be higher in the 60-min-group as compared to those in the 15-min-group. Similarly the levels of paracetamol in CSF in the time interval between 150 to 210 minutes were higher in the 60-min-group as compared to those in the 15-min-group. The elimination half-life of the drug was found to be longer (median+/-SD) 176± 127.62min in 60-minutes-group as compared to 120± 28.72 min in 15-min-group ($p<0.03$). The maximum plasma concentration (C max) was (median+/-SD) 35.1± 17.48mg/lin the 15-min-group and 37± 7.42 mg/l in the 60-min-group ($p<0.5$). The clearance (Cl) was higher in the 15-min-group [(median±SD) 181+/-67.02 ml/l] as compared to that in the 60-min-group [94.9±45.73 ml/l]. The difference between the clearance was significant ($p<0.01$). The volumes of distribution at steady state (Vss) were (median±SD) 31.5±8.46 l in 15-min-group and 25.2±8.18 l in the 60-min-group ($p<0.1$).

4.2 Comparison with current literature

The response to the administration of paracetamol is not directly related to the concentrations of the drug in blood but rather to an effect compartment. There exists a time delay before the drug reaches the effect compartment and the equilibration half-time (Teq) is approximately 1h. The effect compartment does not have real measurable concentrations, but concentrations equate approximately to those observed in the CSF. The speed of onset may be shortened by giving a lager initial dose or improving the absorption characteristics (Anderson & Gibb, 2007b). In our experiment after the i.v.

application of 1g paracetamol the elimination half-life of paracetamol in plasma was 120± 28.72 min. and after the application of the drug (1g) over 60 minutes it increased to 176±127.62min.The increase in the elimination half-life achieved after an intravenous infusion of paracetamol applied over a longer period of time results in a prolonged presence of the drug in plasma and effect compartment leading to an increased duration of its effect.

A recent study (Juhl *et al.*, 2006) performed to demonstrate the analgesic efficacy of intravenous paracetamol 2 g as compared to the recommended dose of 1 g reports that the analgesic efficacy of a 2 g starting dose of IV paracetamol was superior over the recommended dose of 1 g in terms of magnitude and duration of analgesic effect for postoperative pain following third molar surgery, with no significant difference between groups regarding safety. Beck (Beck *et al.*, 2000) also demonstrated that after the rectal application of paracetamol the analgesic doses of paracetamol can only be achieved after administration of twice the conventional dose. The application of higher doses results in higher levels of the drug in plasma and also in the effect compartment. That may result in a longer elimination half-life leading to the required analgesic effects.

The results obtained from our study indicate that the dosage and time of application of i.v. paracetamol to achieve higher and prolonged concentrations of the substance in plasma and effect compartment needs optimization. Increasing the initial dose of i.v. paracetamol followed by increased repeated doses is reported to be beneficial for the immediate postoperative period.

In a study Gregoire (Gregoire *et al.*, 2007) and colleagues demonstrated that a higher dose could be of interest in the immediate postoperative period when the pain is maximal. They used an initial dose of 2g i.v. paracetamol followed by 1g doses every 6 h, leading to a total of 5 g in 24 h. Following the first 15-min i.v. administration of paracetamol 2 g, plasma concentrations ranged from 67.9±21.8 µ/ml (peak plasma concentration (C(max)) at the end of infusion) to 6.2±2.3 µ/ml (trough plasma concentration (C(min)) measured just before the next infusion). After the repeated 1g infusions, the plasma concentrations were approximately 35% lower than that measured after 2g,

In our study the median values of C(max) were 35,1mg/l in the 15-min-group and 37mg/l in the 60-min-group. The median values of C(max) of paracetamol in both groups were comparable and we used a similar dose of 1g in both the groups and the mode of application was i.v. infusion. The administration of the drug as multiple bolus doses or as an infusion over longer period of time may result in the presence of the drug in plasma for a prolonged time.

Previous reports indicate that the analgesic effects of paracetamol correlate with an effect compartment rather than to the plasma levels of the drug. Bannwarth and colleagues (Bannwarth *et al.*, 1992) measured the plasma and CSF concentrations of paracetamol after a short intravenous infusion of Propacetamol. The maximum CSF concentrations were observed at the 4^{th} hour and the elimination half-life was calculated to be shorter in plasma (2.4h) than in CSF (3.2h), suggesting a possible parallel time course of the drug in CSF to the analgesic effect.
Our results also support an effect compartment and fit in a two compartment model for the pharmacokinetics of paracetamol and the maximum CSF concentrations of paracetamol were observed at the 3rd hour. The mean elimination half-life of the drug in plasma was found to be 2.1h and 3.6h in 15-min-group and 60-min-group respectively.
Bannwarth applied a single dose of 1g paracetamol (Propacetamol 2g) over a period of 3 minutes and plasma and CSF samples were taken from 20 minutes to 12hours. Although we used a different infusion rate and the experiment was carried out on animals, but comparable results were obtained.

According to our results the application of i.v. paracetamol over 60 minutes instead of 15 minutes results in the presence of the drug in the effect compartment for a prolonged period and may produce a better pain management in the postoperative phase.

4.3 Impact of the results

The adequacy of postoperative pain control is one of the most important factors in determining when a patient can be safely discharged from the outpatient facility ((Chung *et al.*, 1997).
The opioid analgesics have been the main drugs used for the treatment of peri operative pain. However, large doses of opioid analgesics can be associated with an increased incidence of the postoperative complications e.g. respiratory depression, sedation, postoperative nausea and vomiting, pruritus, difficulty voiding, and ileus. It results in a delayed discharge from the hospital and with that associated increased total cost of treatment. The intraoperative use of large bolus doses or continuous infusions of potent short-acting opioid analgesics (e.g., alfentanil and remifentanil) may actually increase postoperative pain as a result of their rapid elimination and the development of acute tolerance (Guignard *et al.*, 2000).

Therefore the use of non-opioid analgesics as an adjuvant or as a mono therapy during the perioperative period is getting increasing popularity among the anaesthesiologists practicing in the ambulatory environment.
The inadequate treatment of postoperative pain contributes to the patients suffering and may prevent rapid recovery and rehabilitation. An understanding and application of the basic principles of pain management can provide adequate analgesia for the majority of postoperative patients (d'Amours & Ferrante, 1996). The optimisation of postoperative pain treatment is therefore an important part of the therapeutic management.
Considerations regarding the side effects of the individual analgesics like nausea, and respiratory depression lead to the inadequate doses of analgesics resulting in unnecessary patient suffering. In a French study performed in 96 clinics it was noted that 46.4% of postoperative patients suffered from severe pain; due partly to the sub therapeutic doses of opioid analgesics in at least 10% of patients and over half of the patients the interval between doses was too long (Poisson-Salomon *et al.*, 1996).

The onset of analgesic action is an important factor when characterizing the clinical efficacy of analgesics, especially in the management of postoperative pain (Laska *et al.*, 1991).
The improvement in the management of postoperative pain leads to the reduction of postoperative morbidity. By reducing the complications associated with inadequate postoperative pain management, the hospital stay and the total cost of treatment can be reduced (d'Amours & Ferrante, 1996; Kehlet, 1997).

The presently available data includes the studies showing the optimization of postoperative pain management. However, none of them show the optimization of analgesia through different infusion protocols. The studies concerned with the pharmacokinetics of paracetamol are still to be confirmed in human and animal models.
The evaluation of the pharmacokinetics of i.v. paracetamol in our study show that the application of 1g of the drug as an intravenous infusion over 60 minutes as compared to that over15 minutes is associated with a prolonged elimination half-life of the drug in plasma and higher levels of the drug in CSF. As current studies suggest CSF to be the effect compartment for the analgesic effects of paracetamol (Bannwarth et al 1992); optimisation of the intravenous application to obtain an increased CSF concentration may be of value for a better utilization of pharmacological effects of the drug after intravenous application; especially for postoperative analgesia.

4.4 Limitations

The study did not include the measurement of analgesic or antipyretic effects and the results obtained from an animal experiment model may not be applied to a human model but the data obtained from animal experiments may be beneficial for further studies in human.

The flow of CSF was reduced to a very low level after 210 minutes that no further collection of CSF samples was possible. Similarly the samples of

plasma were not taken for a longer period than 210 minutes. The concentration of paracetamol measured with this method was not possible under the limit of the used procedure.
For the most exact calculation of half-life kinetics long lasting measures of blood concentrations of the drug till it reaches the limits of the detection are useful.

4.5 Conclusion and perspectives

The infusion of 1g i.v. paracetamol over a 60 minutes period instead of recommended time of 15 minutes results in a higher plasma and CSF concentration. Pharmacokinetic suggests that, the analgesic effect of i.v. paracetamol for an infusion over 60 minutes is superior to the recommended infusion over 15 minutes. The infusion protocol for patients´ treatment should be scrutinized in randomized clinical trials.
According to the results obtained from our study, the application of i.v. paracetamol for a longer duration of time for example over 2 hours instead of 15 minutes may result in a longer period of analgesia. Increasing the dose of paracetamol from 1g to 2g may also produce better pain management.
Further randomized clinical studies in humans should be performed to confirm the results achieved from animal trials.

5 Abstract

Introduction:

Perfalgan® is a newly developed; direct inject able form of paracetamol. The recommended infusion rate for Perfalgan® is 1g over 15 minutes. This recommendation is based on the rationale that paracetamol acts centrally and to achieve an efficacious cerebrospinal fluid (CSF) level of paracetamol a high gradient between plasma and liquor is essential.

Aim of the trial:

Aim of the present investigation was to evaluate, whether similar efficacious CSF levels of Perfalgan® could be obtained after an infusion rate of 1g over 60 minutes.

Methods:

Experiments were performed in 10 anaesthetized female German domestic pigs. The pigs were randomized either in the group with an infusion rate of 15 minutes (n=5) or 60 minutes (n=5). In the 15-minutes-group plasma and CSF samples were taken 15, 30, 60, 90 120, 150, 180, and 210 minutes after starting the infusion. In the 60-minutes-group plasma samples were taken 60 minutes after starting the infusion and every 30 minutes up to 210 minutes. CSF samples were obtained after 90, 120, 150, 180, and 210 minutes.

Results:

There were no differences between the groups regarding age (15-min-group: 11 - 13 weeks; 60-min-group: 11 - 14 weeks) and body weight (15-min-group: 38.8 – 41.7 kg; 60-min-group: 38.5 – 41.9 kg).

The elimination half-life (t ½ beta) of the drug was found to be longer in 60-minutes-group [(median±SD) 176± 127.62min] as compared to that in 15-min-group [120± 28.72 min]. The clearance (Cl) was lower in the 60-min-group [(median±SD) 94.9±45.73 ml/l)] as compared to that in the15-min-group [181±67 ml/l]. The values of maximum plasma concentration (C max) were (median±SD) 35.1± 17.48 in the 15-min-group and 37± 7.42 mg/l in the 60-min-group. The volumes of distribution at steady state (Vss) were (median+/-SD) 31.5±8.46 l in 15-min-group and 25.2±8.18 l in the 60-min-group.

Our results indicate that plasma levels are higher in the 60-minutes-group as compared to that in 15-minutes-group in the time interval between 60 and 180

minutes after starting the infusion. In the time interval between 90 and 210 minutes CSF levels were similar in both groups.

Conclusion:

The intravenous infusion of 1g paracetamol over a period of 60 minutes instead of recommended duration of 15 minutes results in higher plasma and CSF concentrations. Pharmacokinetics suggests that, the analgesic effect of paracetamol for an infusion over 60 minutes is superior to the recommended infusion over 15 minutes. The infusion protocol for patients´ treatment should be scrutinized in randomized clinical trial

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in Lahore, Pakistan:

Ahmad, Ahsan Siddiqui,Gardezi, Iftikhar, Khan, Latif, Naru, Nawaz, Qudsia, Ullah, Ul-Hassan, Ul-Haq, Waheed.

in Marburg:

Lennartz, Wulf, Maisch, Rothmund.

Danksagung

Mein besonderer Dank gilt meiner Familie, ohne deren Unterstützung und Vertrauen diese Arbeit nicht möglich gewesen wäre.

Herrn Prof. Dr. med. H. Wulf, Direktor der Klinik für Anästhesie und Intensivtherapie des Universitätsklinikums Marburg, gilt mein Dank für die Überlassung des Themas und seine wissenschaftliche und materielle Unterstützung, durch die diese Arbeit erst ermöglicht wurde.

Herrn Prof. Dr. med. U. Kroh und Herrn Dr. med. T. Vassiliou möchte ich meinen besonderen Dank aussprechen, da sie diese Arbeit stets durch ihre organisatorische, kompetente, wissenschaftliche Anleitung und fruchtbare Diskussion gefördert und begleitet haben.

Ich danke Frau Dr. med. univ. C. Rolfes und Herrn Prof. Dr. med. L. Eberhart für ihre Diskussions- und Hilfsbereitschaft.

Des Weiteren danke ich insbesondere Herrn Dr. med. T. Steinfeldt und Herrn A. Gockel für ihre Hilfsbereitschaft bei der Durchführung und Umsetzung der Arbeit.