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The absorption of gabapentin following high dose escalation

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Gabapentins (GBP) is structurally similar to GABA yet its mode of action remains uncertain. It is water-soluble and GI tract absorption occurs via the L-amino acid transport system in the proximal small bowel. It has been suggested that this transportation is capacity limited, thus decreasing GBP bioavailability at higher doses. GBP is not protein bound, therefore, salivary levels might be expected to be similar to those in serum; also the drug does not induce hepatic enzymes and is excreted unmetabolised by the kidney. Within the dose-range normally prescribed, it is devoid of pharmacokinetic (PK) drug interactions with all other anti-epileptic drugs.

This study assesses two things in patients with epilepsy: (a) bioavailability of higher doses of GBP (1200–4800 mg per day), and (b) the influence of high dose GBP on between-dose serum concentrations of co-prescribed anti-epileptic drugs. After stabilising at each dosage, a sequence of serum and saliva samples were collected within the dosage interval; GBP and co-medication concentrations were determined and the results subjected to PK modelling.

Meaned results from 10 patients indicate that GBP continues to be absorbed in a reasonably linear manner relative to dose up to 4800 mg per day. The study also shows that GBP is transported into saliva, however, salivary concentrations are only 5–10% of those in plasma. Furthermore, the results indicate that GBP, in higher than recommended doses, did not change plasma concentrations of lamotrigine, carbamazepine, carbamazepine-epoxide, vigabatrin, primidone, phenobarbitone or phenytoin when added to treatment.

It is concluded that larger than recommended doses of GBP can be efficiently absorbed by some patients and also that GBP plasma levels do not fluctuate greatly between dosage intervals, therefore, twice daily dosage is a possibility.

Key words: gabapentin; pharmacokinetics; high dose absorption.

INTRODUCTION

Gabapentin (GBP) is a relatively new anti-epileptic drug that is structurally similar to GABA and is approved as add-on therapy for treatment of partial seizures with or without secondary generalisation. Its mode of action remains unclear[1, 2]. Following initiation of treatment the dose can be escalated quite rapidly with a recommended maximum in adults of 2400 mg per day. The drug is absorbed from the proximal small bowel into the blood stream by the L-amino acid transport system and bioavailability of GBP is reported to be dose-dependent, possibly because the L-amino acid transport system is capacity limited[3, 4]. Peak serum levels of GBP occur 1–2 hours post-ingestion and the drug is subsequently eliminated via the kidneys without metabolism. It is not protein bound. Plasma GBP concentrations are reported to increase linearly with dose up to about 1.8 g per day. Plasma levels continue to increase at higher doses, but less than expected. The non-linear relationship between dose and plasma level is thought to arise from saturable absorption of GBP from the intestine[5], and it is proposed that a maximum dose of about 5 g per day could be absorbed.

More recently, pre-morning dose serum GBP concentrations in 228 patients with epilepsy were studied[6] which showed that individual patients produced a significant correlation between serum level and dose within the daily range of 400–4800 mg. Up to 6 g per day GBP were administered to patients in another recent study[7] and blood was collected for drug determination which showed that serum levels increased at each dose increment, but there was decreased bioavailability at the high doses. Plasma GBP concentrations ranged from 5.9 to 21.9 mg/l (34.5–127.9 μmol/l). It was concluded that high doses of GBP can be absorbed and may be effective in a proportion of patients.

The present study investigates GBP disposition in epileptic patients undergoing escalation to higher doses than currently recommended. It is the first study to provide dose-to-dose pharmacokinetic (PK) evaluation to examine the absorption of GBP following high dose escalation.

For many of the anti-epileptic drugs, salivary concentrations reflect the free (non-protein bound) fraction in plasma and may, therefore, correlate better than total plasma levels with the clinical effects[8]. Furthermore, a strong correlation between saliva and plasma drug levels enables one to consider saliva as an alternative biofluid for therapeutic drug monitoring (TDM) in patients who are averse to venesection. Since GBP is not protein bound[9, 10] it might be expected that salivary levels would be similar to those in serum or plasma. A second objective of this study was to investigate whether GBP is transported into saliva and, if so, to see if a useful relationship exists between plasma and salivary GBP concentrations.

GBP is reported not to interact pharmacokinetically nor to alter serum levels of any other anti-epileptic drugs, but high doses of GBP have not investigated. A further aim of this study was to evaluate the possible effect of such high doses of GBP on between-dose areas under the plasma concentration/time curve (AUC's) of co-prescribed anti-epileptic medication at steady state.

METHODS

Study design

This study was an additional component to the AUS-STEPS trial[11] as approved by the Human Research Ethics Committee of Royal North Shore Hospital, Sydney. The addition of an extra dosage escalation up to 4800 mg per day was appended to the protocol as an amendment after initiation of the AUS-STEPS trial that provided for an 8-week baseline period during which medication remained unchanged and clinical assessments of seizure control and adverse events were undertaken. Each subject then received maintenance doses of GBP, which were escalated at monthly intervals from 1200 to 4800 mg per day (taken as three divided doses) depending upon clinical response and patient preference. Following stabilisation at each new dosage, a sequence of timed blood and matching saliva samples were collected for determination GBP of and co-medication concentrations.

Subjects

Ten subjects who were eligible for inclusion into the AUS-STEPS trial were invited to participate in the additional protocol at the time of recruitment. They were prescribed not more than two anti-epileptic medications at study entry and co-medication remained unchanged throughout.

Protocol

At each baseline study visit, a 10 ml (clotted) blood sample was collected to determine the concentrations of current medication. After completing the 8-week baseline period, further blood was collected before initiating GBP treatment with rapid escalation over 3 days to a dosage of 1200 mg per day (400 × 3) by Day 4. After 4 weeks treatment, the patients returned for clinical assessment and collection of blood and saliva for the PK profile. Blood collection was carried out as follows.

Following an overnight fast, 5 ml blood was withdrawn and allowed to clot after which the current morning dose of GBP was administered (for first test 400 mg) and 5 ml blood was then collected pre-dose and at 1–6 hours post-dose. Each sample was centrifuged immediately after collection and the serum transferred to another tube.

About 1–3 ml of saliva was also collected at the same time by giving the patient a ball of inert thermoplastic to chew, thereby stimulating salivary flow and collecting the saliva in a 5 ml serum tube. All samples were frozen at −20 °C to await drug analysis.

The GBP dose could then be escalated to the next level (1800 mg per day as 600 × 3) depending upon changes in seizure control or the appearance of adverse events. After 4 weeks at the revised dose, the PK profile was repeated as described before, by first collecting a pre-dose blood and saliva followed by hourly sampling after ingesting 600 mg GBP. Depending upon their response to the previous treatment patients could be dose escalated to 2400 mg per day (800 × 3). After 4 weeks stabilisation, the PK profile

was repeated as before with the morning dose being 800 mg GBP following which the dose was escalated to 3600 mg per day (1200 × 3) depending upon the previous response. After 4 weeks stabilisation at the revised dose, the PK profile was again repeated taking care to collect a pre-morning dose sample and the same sequence followed after a morning dose of 1200 mg. Patients could then be dose escalated to 4800 mg per day (1600 × 3) depending upon their clinical response. After 4 weeks stabilisation at the highest dose, a PK profile was repeated by collecting pre-morning dose samples and continuing the sequence as before after a morning dose of 1600 mg.

Drug measurement

GBP was determined by modifying the reversed phase high performance liquid chromatographic (HPLC) method of Hengy and Kolle[12]. The procedure involved adding an internal standard (PD 403609 in acetone) to a small serum or saliva sample, allowing the proteins to precipitate and centrifuging before evaporating the supernatant liquid to dryness. The residue was then derivatised with picrylsulphonic acid following which the reaction was stopped before extracting with hexane. The derivatives were subsequently separated by reversed phase HPLC with detection at 340 nm. Quantification was by reference to calibration standards made by spiking GBP into serum or saliva over the appropriate concentration range. These were carried through the procedure with each lot of analysis and every analytical batch was subjected to quality control at two concentrations.

Concurrent anti-epileptic medication concentrations were determined in the plasma samples by fully validated HPLC and gas chromatographic techniques. When appropriate the concentrations of pharmacologically active metabolites were also determined.

Data analysis

Serum GBP concentration versus time after dose was plotted at each dose in each individual, and the 6 hours AUC was calculated by applying the trapezoidal rule. In addition, the means of all data were calculated in order to arrive at an average result.

The effect of dose on AUC was analysed using a randomised block design. Each of the 10 subjects was considered as a block to account for subject-to-subject variability. The five doses (1200, 1800, 2400, 3600 and 4800) were considered to be the treatment effects. As there was missing data the regression approach to the analysis of the randomised block design was taken[13]. The linearity relationship between the AUC and dose was investigated using linear regression analysis with the test for lack of fit. MINITAB 11 was used for all the statistical analysis.

Salivary GBP concentration versus time after dose was plotted at each steady state dose in each individual and the 6 hours (AUC) was calculated by applying the trapezoidal rule. All data were subsequently meaned in order to arrive at an average result.

Co-medication drug and metabolite concentration versus time after dose was plotted for every dose in each individual, and the 5/6 hours AUC was calculated for each compound by applying the trapezoidal rule. When several patients were prescribed the same drugs the data were meaned in order to arrive at an average result.

RESULTS

Fig. 1 shows the meaned time versus serum GBP profiles for the pooled data from all patients at each dose. Four patients completed the 4800 mg dose schedule whilst six completed the 3600 and 2400 mg and eight completed the 1800 mg.

Data analysis revealed a significant variability from subject to subject ($P < 0.05$) and also that AUC was dependent on the dose ($P < 0.001$). Linear regression of the AUC versus dose data was fitted by a straight line. The repeated values at different doses enabled the study of linear trend, i.e. testing the lack of fit of a linear function. It was found that the linear regression was significant ($P < 0.05$). There was no lack of fit ($P = 0.6495$) which implied the existence of a linear trend, i.e. within the dose-range studied, AUC increased as dose increased.

GBP has a serum elimination $t_{1/2}$ of 5–9 hours and Fig. 1 also shows that at steady state the plasma GBP concentrations fluctuate less than expected between dose intervals. Time to peak concentration is 2–3 hours and with the 4800 mg per day treatment the mean, between-dose GBP plasma level was 13.6 mg/l (79.4 μmol/l) with a SD of only 2.4 mg/l (14.0 μmol/l). The effect is similar to sustained release and probably arises because absorption takes place from the small bowel and is regulated by an active transport mechanism.

Fig. 2 is a plot of meaned AUC at each dosage versus dose and this indicates an essentially linear relationship between AUC and dose throughout the range investigated. The equation of the line is: AUC = $7.64 + 0.0125 \times$ Dose, however, there were substantial inter-individual differences in the dose to serum level relationship which may reflect individual differences in L-amino acid transport capacity.

Fig. 3 shows meaned time versus salivary GBP profiles of the pooled data for all patients at each dose.

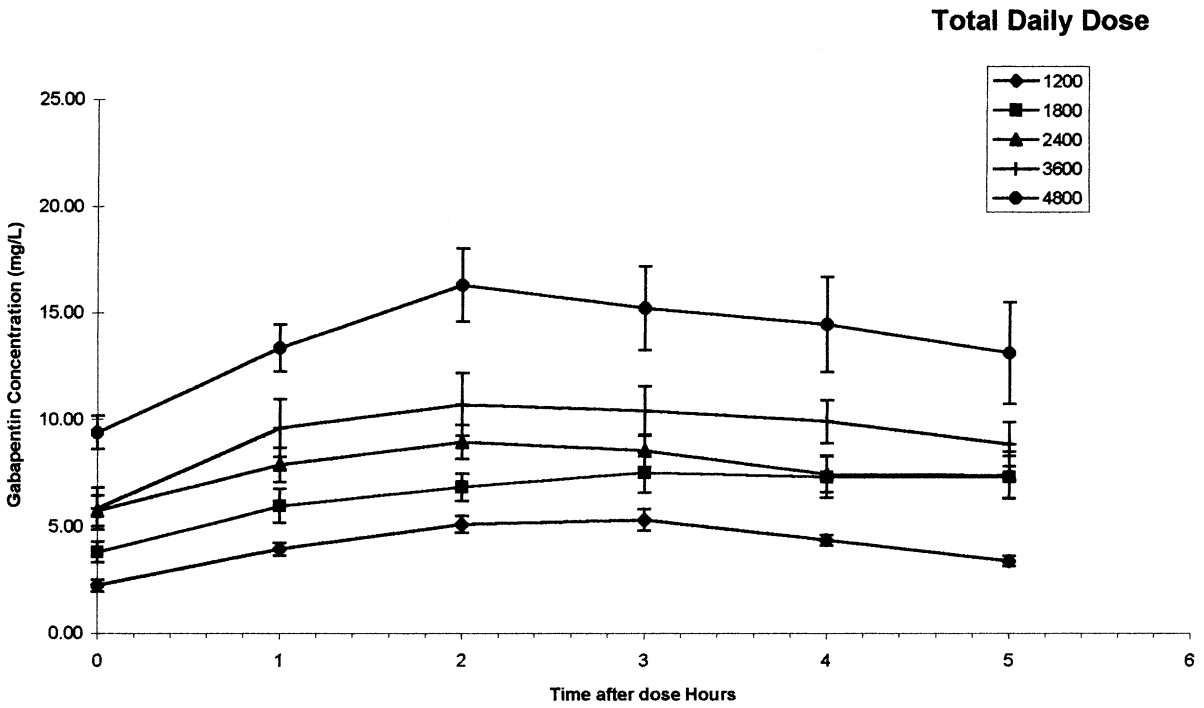

Fig. 1: Meaned time versus serum GBP profiles for the data pooled for all volunteers at each dose (1 mg/l = 5.84 μmol/l). Four volunteers completed the 4800 mg dose whereas six completed 3600 and 2400 mg while eight completed 1800 mg.

Comparing this with the corresponding serum levels enables one to see that the salivary GBP concentrations were only 5–10% of those in serum, but there was substantial inter- and intra-subject variability. Approximately 10% of the saliva samples were either not collected or leaked in transit causing a substantial amount of data to be missing.

Fig. 4 is a plot of meaned salivary AUC at each dosage which indicates a reasonably linear relationship throughout the dose-range investigated, the

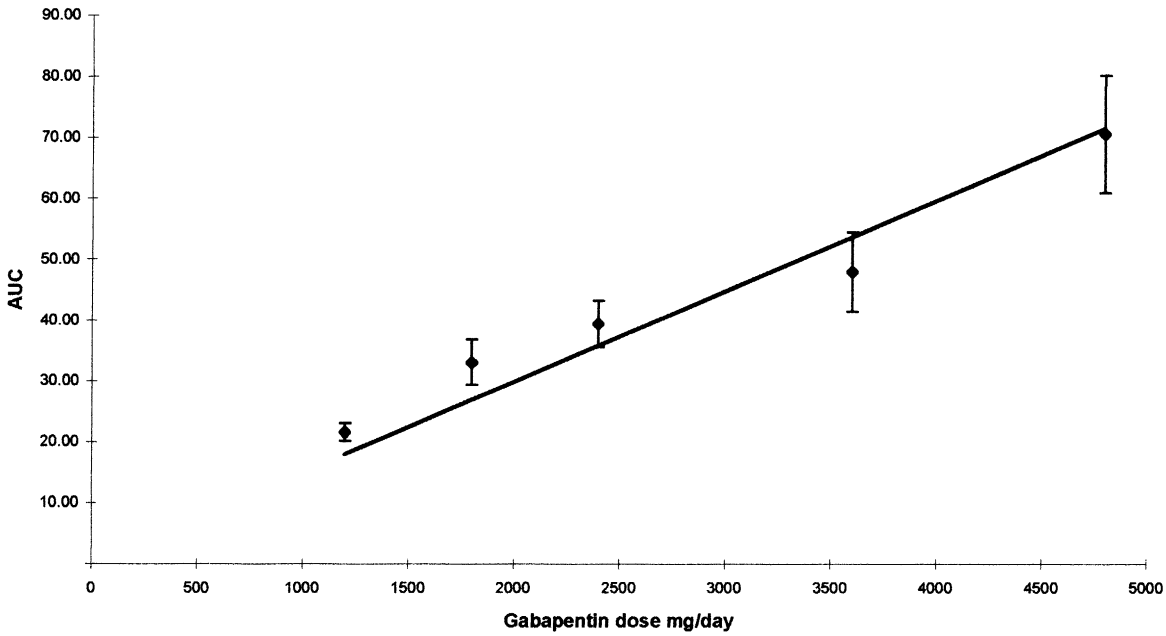

Fig. 2: A plot of meaned AUC $\pm$ SD for all patients at each dosage versus GBP dose (mg per day). The line of best fit is inserted.

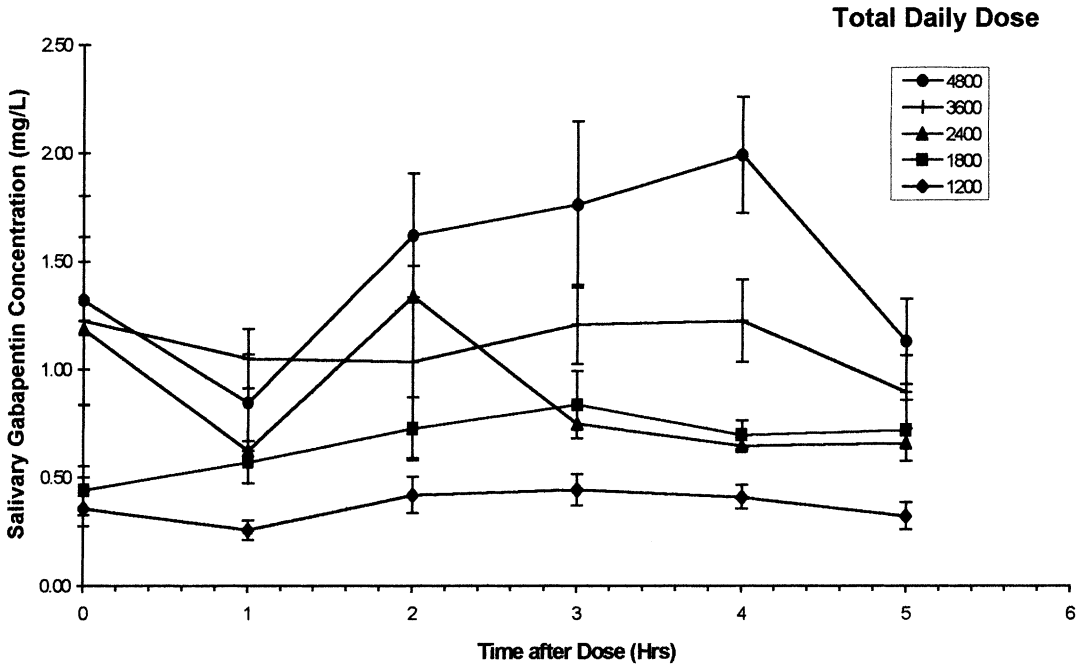

Fig. 3: Meaned time versus salivary gabapentin concentration profiles for the pooled data from all volunteers at each dose.

equation of the line being: AUC $= 0.5095 + 0.0015 \times$ Dose.

Co-medication AUC data could be evaluated in only 8 of the 10 patients that entered the study since two did not escalate above the lowest GPT dose. Between-dose interval co-medication PK studies were performed in those patients who were stabilised on a range of GBP doses while their co-medication remained unchanged. Six patients had PK performed at 1200, 1800, 2400 and 3600 mg per day of GBP and, of these, four also had PK determined at 4800 mg per day GPT. The remaining two patients only escalated GBP to 1800 mg per day. Co-medication prescribed is summarised in Table 1.

Fig. 5 summarises the mean co-medication AUCs at each GBP dose for all patients prescribed phenytoin, carbamazepine, lamotrigine and vigabatrin. For those patients on carbamazepine the epoxide AUCs were

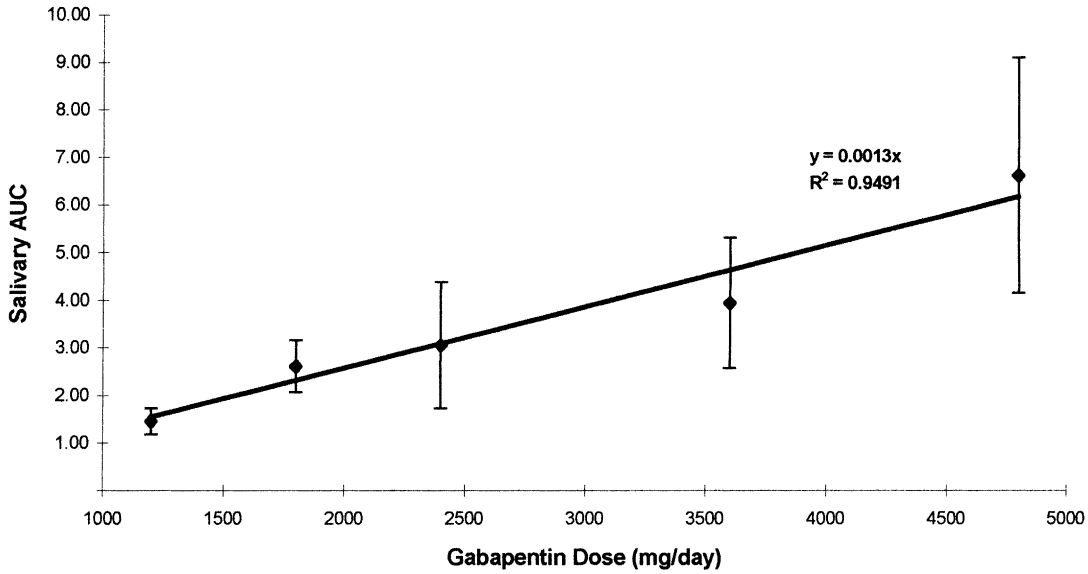

Fig. 4: Meaned salivary GBP AUC $\pm$ SEM for all patients at each dosage versus GBP dose (mg per day).

Table 1:

Drug	Number of patients
Phenytoin	3
Carbamazepine	5
Lamotrigine	2
Vigabatrin	2
Primidone	1

calculated and are shown also. It is evident that the AUC for all these drugs remains constant as GBP doses are increased. One patient (VTC) was prescribed primidone and the AUC for both parent drug together with the metabolite, phenobarbitone, are illustrated (see Fig. 6). These also remained constant throughout the study. The only patient whose serum drug

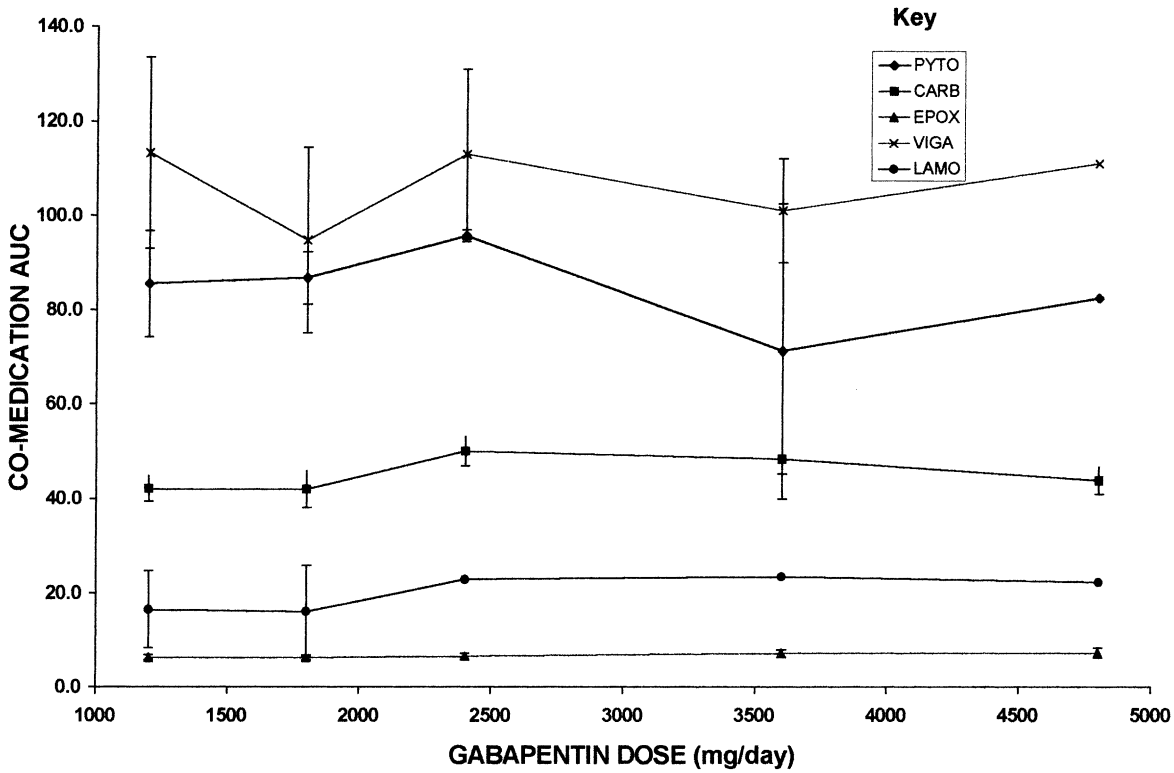

Fig. 5: Mean ± SEM AUC of the various co-medicaments at increasing GBP doses. Key: PYTO, phenytoin; CARB, carbamazepine; EPOX, carbamazepine-epoxide; VIGA, vigabatrin; LAMO, lamotrigine; POBA, phenobarbitone; PRIM, primidone.

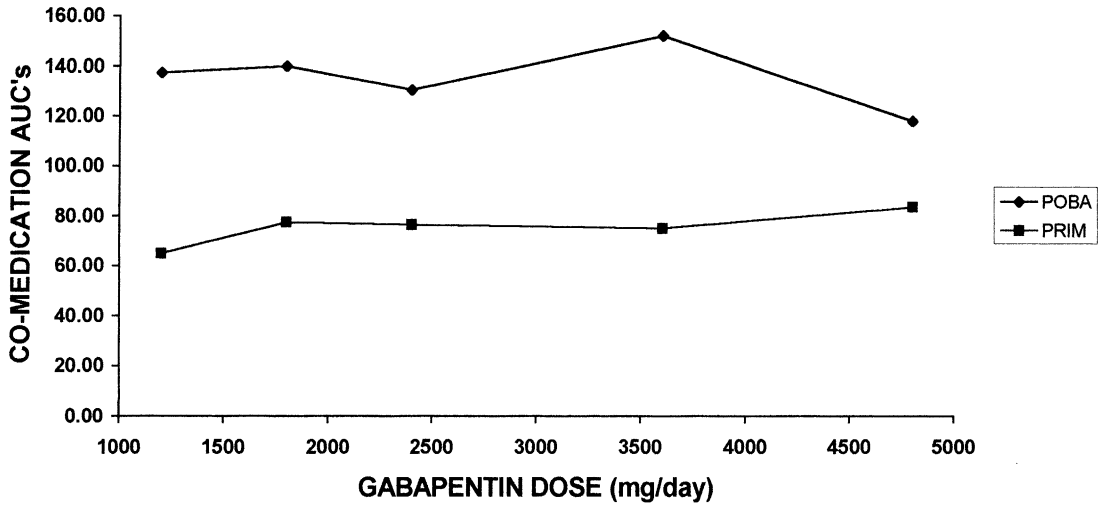

Fig. 6: AUC of primidone and metabolite at increasing GBP doses—patient VTC.

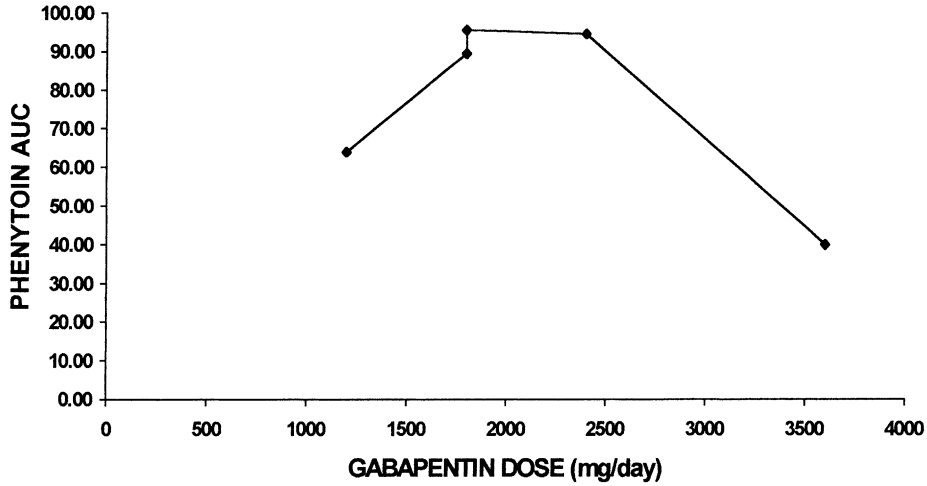

Fig. 7: AUC of phenytoin at increasing pentin doses—patient can.

concentrations changed significantly was CAN (Fig. 7). This patient was prescribed phenytoin alone, however, the serum levels did not change in the other two patients on phenytoin.

DISCUSSION

These data for meaned plasma GBP concentrations, showed a proportional increase in the serum levels with higher doses and a linear increase in AUC with doses up to 4800 mg per day. Furthermore, the variation in serum concentration between dose intervals was less than expected for a drug with an elimination half-life of only 5–9 hours which indicates that the recommended three or four times daily dosing is probably unnecessary.

These results bring into question the concept of a saturable absorption and, hence limited bioavailability of GBP at least up to a dosage level of 4800 mg since there was a linear increase of absorption at the higher dosage in our patients. These findings support those of May *et al.*[6] and Wilson *et al.*[7] and disagree with those of Richens[14], who reported that while bioavailability of single doses ranged from 42 to 57%; this dropped to 35% on a multi-dose regimen of 1600 mg given three times a day.

A possible explanation could relate either to the study population being refractory patients with epilepsy on polypharmacy which might enhance absorption of GBP or there could be an altered L-amino acid transport consequent to epilepsy as compared with that found in the healthy subjects used for phase one PK studies[4]. Alternatively, the proportionally increased absorption might reflect the recruitment of an another absorption mechanism, e.g. passive diffusion.

These findings refute the concept of saturability of absorption, at least to a dosage of 4800 mg and indicate that bioavailability continues to be maintained. Thus, in the absence of clinical efficacy, increasing the dose of GBP in excess of the maximum recommended would be justified. The results bring into question the basis of the recommended upper dose limit of 2400 mg as defined both in the United Kingdom and Australia, and highlights the need to review PKs on an inter-dose approach of some of the new anti-epileptic medications in patients rather than healthy volunteers.

A further aim of this study was to determine whether GBP was transported into saliva in sufficient quantity to allow salivary GBP levels to be measured as an alternative to serum. The results indicate that saliva could provide an alternative vehicle for the determination of GBP levels, however, since salivary concentrations are much lower than those in serum it is important to validate the analytical method over the range of values expected and in the same matrix.

GBP is not protein bound[9, 10], so one might reasonably expect salivary levels to directly mirror those in serum, however, salivary GBP concentrations in this study were only 5–10% of those in serum. Little has been published regarding GBP secretion into saliva, although Taylor[15] stated that the very high hydrophilicity of GBP, with an octanol:water partition coefficient of approximately 0.05, may limit its passage across biological membranes. The present findings agree with the limited information that is available[16] (Bockbrader, personal communication).

Anti-convulsant drug concentrations in CSF are often the same as the unbound fraction in plasma. Earlier studies with GBP in rats have demonstrated that CSF concentrations are also only 5–10% of the

unbound serum fraction[16] and this may also be related to its hydrophilic character[15].

The present study has shown a linear relationship between increasing salivary GBP concentrations and dose up to 4800 mg per day (Fig. 4), however, absorption of GBP into saliva is limited as has been found with CSF[17].

While salivary levels are much lower than those in serum they do provide a means of assessing GBP levels in serum. A limiting factor was the considerable dose-to-dose fluctuation of salivary GBP levels in any individual patient. This suggests that the only pragmatic role for salivary level GBP assessment would be to confirm that the patient has taken GBP rather than to meet the more demanding rigor of therapeutic monitoring in clinical practice.

Regarding the third aim of the study, to assess the effects of higher than normal doses of GBP on co-medication serum levels in a routine clinical care situation, the number of subjects is small, but the detailed assessment of between-dose PK is the most rigorous, thus far undertaken. It has examined PK of concomitant anti-epileptic drugs in patients who were exposed to up to double the recommended GBP dosage. The mean serum AUC graph (Fig. 5) indicates that co-medication bioavailability remains constant with increasing dosages of GBP for phenytoin, carbamazepine, lamotrigine and vigabatrin. Furthermore, the bioavailability of carbamazepine-epoxide, the pharmacologically active metabolite of carbamazepine, did not change. While these findings are those expected from published data on the disposition/PK of GBP[9] we have shown that increasing GBP doses and serum levels up to double the recommended maximum does not alter either the absorption or elimination of a range of common anti-epileptic drugs.

The one confounding patient was CAN (Fig. 7) in whom phenytoin levels fluctuated considerably. This patient's serum concentrations and AUC for phenytoin decreased by 50% at a GBP dose of 4800 mg per day, however, the patient's serum levels had fluctuated at lower GBP doses, raising concerns about compliance. The other two patients on phenytoin did not demonstrate a similar fluctuation.

These findings support the claim that GBP does not cause a PK interaction with other anti-epileptic drugs, therefore, it is unlikely to cause toxicity from concomitant administration, however, a pharmacodynamic interaction may occur.

CONCLUSIONS

This is the first reported study to evaluate detailed inter-dose serum concentration profiles and determine PKs of GBP at five separate dosage levels, in the same patients under routine clinical treatment conditions. In four of six patients the bioavailability of GBP was maintained when the dose exceeded the maximum recommended. Furthermore, despite its rapid serum elimination half-life, it is concluded that it may be possible to dose GBP only twice daily since plasma concentrations do not fluctuate greatly between dose intervals.

The present work proves GBP is transported into saliva and that during maintenance dose salivary GBP concentrations are 5–10% of those in serum although they fluctuate markedly both within and between individuals. Our findings also indicate that there is a linear relationship between GBP salivary levels and dosage increments up to 4800 mg per day. However, the low and fluctuating levels GBP in saliva will only provide a means of confirming that the patient has taken GBP rather than meeting the more demanding rigor of therapeutic monitoring in clinical practice.

Finally, it is concluded that larger than recommended GBP doses do not affect either the steady state serum concentrations or between dose interval AUC's of a range of commonly prescribed anti-epileptic medications or their metabolites.

Therapeutic monitoring of GBP maybe somewhat controversial, but several reports[18–22] suggest it may be beneficial during individualisation of GBP treatment and it would certainly help to identify those patients who are able to absorb more than the currently commended maximum dose and the potential clinical benefit which might accrue from this. In addition it will identify unexpected accumulation of GBP in cases where a disturbance of renal function has been previously unsuspected.

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