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Original Research Article

Therapeutic follow-up of postoperative patients on tramadol in the intensive care unit a tertiary African hospital: a cohort study

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ABSTRACT

Background: Tramadol, an analgesic, is a prodrug requiring bioactivation through cytochrome P450 enzymes (CYP450) to obtain O-desmethyltramadol (M1), its active metabolite. However, little is known on the African pharmacogenetic profile of tramadol metabolism. Hence, we aimed to study the biological efficacy of tramadol in an African population.
Methods: This was a prospective cohort study over a 3-month period carried out at intensive care unit of a Cameroonian tertiary hospital. We enrolled patients with moderate-to-severe pain surgery, who had not been administered drugs metabolized by CYP450. Immediately after surgery, 2 mg/kg of tramadol was administered intravenously every 6 hours. Pain was assessed using the visual analog scale (VAS) within the first 24 hours. Vital signs and side effects were recorded. Plasma samples were collected at 3rd and 6th hours to assay tramadol and M1 using HPLC-UV.
Results: We enrolled 30 patients with a mean age of 32 years operated for caesarean section, laparotomy and cancer surgery, under spinal and general anesthesia. Before administration of tramadol, the VAS was 6/10. The VAS decreased 4/10 to 1/10 between the 3rd and the 6th hour. There was a reduction of the respiratory rate of 3 breath cycles per minute as early as the 6th hour. Samples from 13 patients were analyzed. M1 was found in all patients; of which 4 had a slow metabolism and 3 had a faster metabolism.
Conclusions: Overall there was good correlation between the clinical and biological analgesic efficacy of tramadol.

Keywords: Tramadol, M1, Therapeutic follow-up, Postoperative pain

INTRODUCTION

Postoperative pain is considered an undesirable and expected effect of surgery, hence, an effective postoperative analgesia regimen is considered indisputable. Tramadol is an effective analgesic for the relief of moderate to severe postoperative pain.[1] It has an original action profile on both weak opioid agonist on μ receptors, and as a reuptake inhibitor of norepinephrine and serotonin.[2] Tramadol is a prodrug that requires bioactivation to obtain O-desmethyltramadol (M1) which has the analgesic effects of tramadol. This bioactivation is done through the hepatic enzyme (CYP2D6) of the cytochrome P450 family which has genetic

polymorphisms. In the Caucasian population, 10% of people do not have CYP2D6 activity. Thus, tramadol will have no analgesic effect on them.[3-5] However, the pharmacokinetic and pharmacodynamic profiling of drugs ensures their rational use, providing a precise description of the dose-concentration-effect-toxicity relationships.[6] In our setting, few studies have been conducted on the clinical and pharmacological monitoring of analgesic drugs. Hence, we carried out this study on the therapeutic follow-up of tramadol in patients admitted in the postoperative period, in the intensive care unit (ICU) of the Yaoundé Gyneco-obstetrics and Pediatric Hospital (YGOPH).

METHODS

This was a prospective cohort study conducted over a 3-month period from February 2016 To April 2016 in the ICU of YGOPH, as well as in two laboratories. Sampling was consecutive and non-exhaustive. We included patients who underwent surgeries of moderate to severe pain, without altered consciousness, with no notion prior administration of drugs metabolised by CYP450 enzymes and with no hepatic or renal failure.

Clinical evaluation

Sociodemographic data, the type of surgery and the technique of anesthesia were studied. Tramadol was administered over 15 minutes at a dose of 2 mg/kg intravenously diluted in 100 ml of infusion every 6 hour. Pain assessment with the visual analogue scale (VAS) was done at admission into the ICU and then at the 20th min, 3rd hour, 6th hour, 12th hour, and 24th hour, respectively, following tramadol administration. Clinical parameters and side effects were recorded. We collected 3-5 ml of blood sample in EDTA tubes at the 3rd and 6th hour after administration of tramadol.

Laboratory analysis

The collected blood was centrifuged for 20 minutes at 4000 rpm to extract the plasma in search for M1.

Plasma pre-treatment: Liquid-liquid extraction

In 500 µg of plasma, we added a drop of 0.1 mol/l NaOH. The mixture was vortexed for one minute. We added 1 ml of extracted solvent which was made of ethylacetate+cyclohexane in the ratio of 1:4. The mixture was vortexed second time for one minute and then centrifuged at 400 rpm for 15 minutes. The organic phase obtained was then transferred to vials to be introduced into the autosampler.

Preparation of the HPLC

We used an HPLC-UV chain with RP C-18 tubes with 5 µm particles, 250×4.6 mm Phenomenex® brand. The eluent or mobile phase was acetonitrile or phosphate buffer (KH_2PO_4 0.01 M solution) in proportions: 30/70 which was then mixed with triethylamine at a concentration of 0.1% TEA. The pH of this mobile phase was adjusted to 3. The injection volume was 10 µl with a flow rate of 1 ml/min and a separation time of 7 minutes. The detection was set at 218nm UV at room temperature.

The data obtained was analyzed on the software SPSS version 20 and Epi Info version 3.5.4. The statistical study was descriptive with the study of proportions and means.

RESULTS

Socio-demographic and clinical data

We recruited 30 patients with a mean age of 32.8±10.26 years. The American Society of Anesthesiologists 1 patients (60%) were the most represented. Caesarean section was the most performed surgical procedure (80%), followed by laparotomies (ectopic pregnancy and pelviperitonitis) and gynecological carcinological surgeries. Spinal anesthesia (RA) was the most commonly performed anesthesia technique (54%) followed by general anesthesia with orotracheal intubation (AG+IOT) in 43% of patients.

The modalities of administration of tramadol

Tramadol was averagely administered at a dose of 100 mg/kg intravenously every 6 hours. It was always used in balanced analgesia with level 1 analgesics, mainly paracetamol (70%).

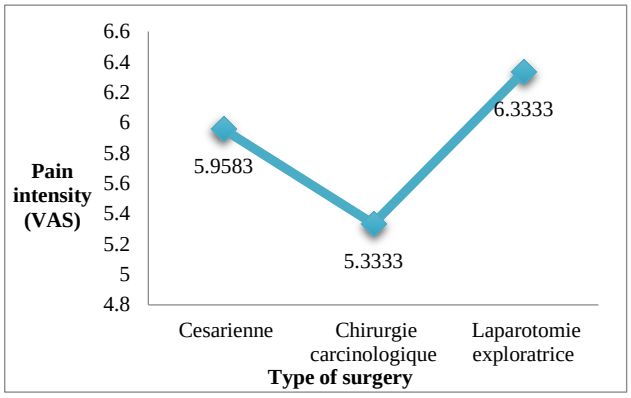

Figure 1: Evaluation of pain intensity before tramadol administration with respect to the type of surgery.

Assessment of pain before tramadol administration

When evaluating the pain intensity of patients prior to tramadol administration, the mean VAS was 5,933±1,257. The intensity of the pain was higher in patients who underwent exploratory laparotomy (6.3/10) (Figure 1). When the vital signs were taken, the respiratory rate was

the only slightly elevated parameter varying up to 25 cycles/min (Table 1).

Assessment of pain following tramadol administration

After administration of tramadol, a reduction in pain intensity was observed as early as the 20th minute. This reduction was 2 points or around 3/10 for all patients at the 3rd h compared to the intensity of the pain before the administration of tramadol. From the 24th h, theVAS was about 1/10 (Figure 2).

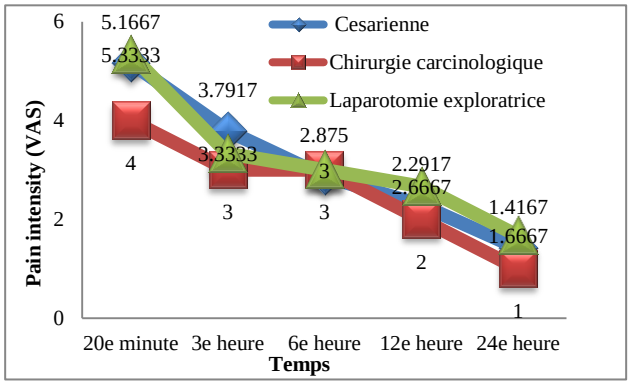

Figure 2: Evaluation of intensity after tramadol administration.

During the evaluation of the parameters, a decrease in systolic blood pressure of 20 mmHg was observed at the 3rd hour and 6th hour respectively for patients who underwent an exploratory laparotomy and a carcinological surgery. Concomitantly, regression of 10 mmHg was recorded for diastolic blood pressure. We observed a regression of 2 to 3 respiratory cycles per minute for all patients and 10 beats per minute reduction inpulse rate.

The main adverse effects of tramadol concerned mainly the gastrointestinal tract (30% of nausea cases and 13.30% of vomiting cases), followed by cholinergic effects (dryness of mouth in 16.7% of cases) and neurological effects especially vertigo (3.30%).

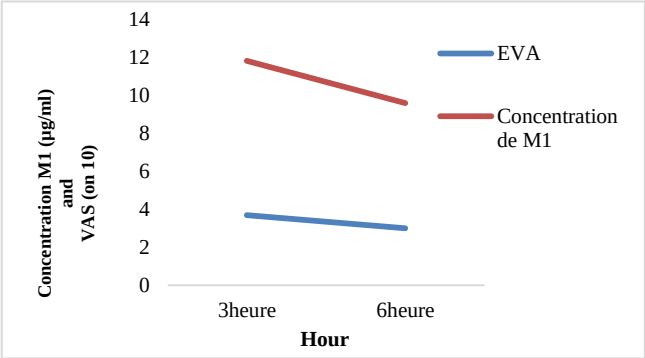

Figure 3: Relationship between the VSA and M1 concentration.

Plasma determination of M1

When we performed the plasma determination of 13 patients. We found the active metabolite of tramadol as M1. Overall, there was good agreement between clinical and laboratory data (Figure 3). However, four patients had a slower metabolism (Table 2); three patients had a faster metabolism (Table 3).

Table 1: Assessment of clinical parameters prior to tramadol administration.

Parameters	Mean	Ecart-type	Minimum	Maximum
SBP (mmHg)	124.4667	15.2694	100	165
DBP (mmHg)	75.3333	12.455	50	100
HR (beats/min)	85.1	15.4124	52	120
RR (cycles/min)	21.7667	4.2074	14	35

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: Respiratory rate; HR: Heart rate.

Table 2: Relationship of VAS and biological assay in patients with slow metabolism.

	Patient 1	Patient 2	Patient 3	Patient 4
VAS at the 3rd hour	7	5	6	4
VAS at the 6th hour	5	3	5	3
M1 concentration at the 3rd hour (µg/ml)	3.28	12.53	13.53	15.53
M1 concentration at the 6th hour (µg/ml)	3.15	11.82	35.11	24.43

Table 3: Relationship between VAS and biological assay in patients with rapid metabolism.

	Patient 1	Patient 2	Patient 3
VAS at the 3rd hour	4	6	5
VAS at the 6th hour	1	5	5
M1 Concentration at the 3rd hour (µg/ml)	14.53	16.53	17.53
M1 Concentration at the 6th hour (µg/ml)	3.53	2.46	1.96

DISCUSSION

The average age of our patients was 32.8±10.26 years, which corresponds to the generally young age of the Cameroonian and African population. Caesarean sections were most performed surgical procedures explained by the fact that the study setting is a hospital specialized only in the managementof mother and child pathologies.

Paracetamol was the main analgesic used in combination with tramadol. In effect, the pain after caesarean section, exploratory laparotomy or cancer surgery is classified as strong in the first 48 hours according to the WHO.[7] As such, it seems logical to propose tramadol as part of a balanced intravenous analgesic regimen.[2] In addition, with respect to the combination of tramadol+paracetamol (acetaminophen), a meta-analysis of randomized clinical trials conducted on postoperative dental, orthopedic and gynecological pain showed the analgesic superiority of tramadol-paracetamol compared to the either analgesic effect tramadol or paracetamol.[8]

The mean VAS before tramadol administration was 5.933±1.257/10, explained by the fact that preemptive analgesia was started during the intraoperative period. A significant reduction in pain intensity was observed for all patients at the 3rd hour compared to the intensity of the pain before administration of tramadol. This reduction is more than 50% at the 24th hour compared to the baseline VAS before administration of tramadol. This threshold significance was proposed in 2003. These data seem to be in agreement with the pharmacokinetic data with respect to the time of action, the half-life and the plasma peak of tramadol.[6]

With regards to the side effects of tramadol, we mainly found the gastrointestinal (nausea, vomiting), cholinergic effects (dryness of mouth) and vertigo. This finding concurs with that of the literature.[9] Of the 30 patients enrolled, 13 had postoperative biological monitoring of the concentration of tramadol and M1 at the 3rd and 6th hour after administration of tramadol. Overall, there was good agreement between clinical and biological parameters. An African study in Ethiopia was previously performed without the biological assay of tramadol.[10] Our results are in line with this study as far as patient satisfaction is concerned.

We wanted to go further than this by testing the hypothesis that patient satisfaction using VAS may be consistent to some extent with the biology of tramadol and M1. We found that those who metabolize slowly have better satisfaction with the analgesic effect. On the other hand, in those who seemed to metabolize rapidly, the VAS decreased but remained generally at levels of moderate pain values. This is in good correspondence with the literature on the subject.[11]

We will have been able to have more samples tested, to measure more specific pharmacokinetic parameters such as the area under the curve, the plasma clearance and the half-life, for example.[11] Nevertheless, our results allow us to know the metabolism profiles (CYP 2D6) of our patients indirectly. In addition, tramadol and paracetamol combination could compensate for the effect of tramadol on VAS values, if tramadol shows low plasma concentrations at the same time.

CONCLUSION

In our cohort made up of a young population, we obtained a good analgesic efficacy of tramadol at the biologically and clinically; highlighting the metabolic profile of our patients.

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