Parenteral versus Oral Route Increases Paracetamol Efficacy

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Summary

The analgesic efficacy and tolerability of parenteral versus oral paracetamol 1g were compared in 323 patients immediately after a hallux valgus plasty performed with local anaesthesia (31 men, 292 women, mean age 52 years). Using a multicentre, double-blind, double-placebo, randomised, parallel-group design, the effects of a single dose of propacetamol (PR) 2g (= paracetamol (PA) 1g), oral PA 1g and placebo (PL) were compared in the recovery room 5 hours (mean) after surgery in three parallel groups of patients with at least moderate pain on a 5-point verbal scale. Efficacy was assessed on pain scores rated on a 5-point verbal scale before administration (T0) and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 and 6 hours after administration and with an overall efficacy 5-point verbal score. Any adverse effects were recorded throughout the duration of the study. PR was statistically superior to PL on pain intensity difference (PID) from T30 minutes to T6 hours (Dunnett test), on maximum pain intensity difference (MAXPID) [p < 0.05] and summed pain intensity difference (SPID) [p < 0.05]. PA was statistically superior to PL at T1, T2, T4, T5 hours (Dunnett test), on MAXPID (p < 0.05) and SPID (p < 0.10). PR was statistically superior to PA on PID from T30 minutes to T4 hours, on MAXPID (p < 0.03) and SPID (p < 0.01). Overall efficacy was found by the patients to be superior with PR vs PA (p < 0.01), PR vs PL (p < 0.05), and PA vs PL (p < 0.10). The remedication time was significantly different between the three groups (p < 0.05). 10 patients experienced 1 adverse effect, PR: 3 (injection site pain, headache, vomiting), PA: 6 [nausea, tremor, injection site pain (3), malaise], PL: 1 (injection site pain). In conclusion, PR 2g (i.e. PA 1g) provided a significantly greater and longer analgesic effect than the same dosage in oral form.

Paracetamol is usually considered a mild oral analgesic in comparison with other oral analgesics. The drug is one of the oral analgesics used in clinical trials as a standard treatment (downside sensitivity), and it has already been shown to be effective in different postsurgical models, especially in orthopaedic postoperative pain.1-3

One of the main reasons for prescribing paracetamol in a postoperative setting is its tolerability.1-3 However, until now its use has been limited to indications with moderate pain or as second-line treatment as injectable analgesics administered some days after surgery. With the availability of an injectable form, paracetamol could be used earlier in the course of the postoperative period when oral administration is prohibited. Furthermore, it could,
Efficacy of Oral vs Parenteral Paracetamol

**Fig. 1.** Structural formula of propacetamol.

Propacetamol (Laboratoires UPSA, Rueil-Malmaison, France) is an injectable produg of paracetamol (fig. 1). The hydrolysis of the ester function due to nonspecific plasma esterases is complete and the intravenous administration of 1g of propacetamol hydrochloride yields 0.5g of paracetamol. Therefore, the toxicity of propacetamol is almost identical to the well established toxicity of paracetamol.

Propacetamol 2g has been shown to be superior to placebo from 1 to 6 hours after surgery\(^4\) and as potent as 1.8g of intravenous lysine acetylsalicylate\(^5\) or 30mg intramuscularly of pentazocine after orthopaedic surgery.\(^6\) It was also found to be as potent as diclofenac 75mg after orthopaedic surgery, and as potent as morphine 10mg after third molar surgery.\(^7,8\) After propacetamol intravenous injection, paracetamol was shown to cross the blood-brain barrier easily\(^9\) and to have a central analgesic effect in healthy volunteers, in contrast to aspirin, which had none.\(^10\) Propacetamol has also been studied in children\(^11-14\) and in other postoperative situations in adults.\(^15-23\)

Some recent data\(^10,24,25\) obtained in healthy volunteers on an experimental pain model (RIII reflex) after intravenous administration of propacetamol indicated that an injectable form of paracetamol would be able to provide better efficacy than an oral form. After Piletta’s demonstration of a central effect,\(^10\) Luthy et al. have shown that the paracetamol plasma peak (after intravenous injection), and not the average plasma plateau, influences this central analgesic effect of paracetamol.\(^24\) In addition, Piguet et al. have shown a lack of ceiling effect with propacetamol 1, 2 and 4g,\(^25\) whereas a ceiling effect was demonstrated with an oral form.\(^26\)

Our goal was to compare the analgesic efficacy of the same dose of paracetamol by the oral or parenteral route in patients with at least moderate pain following surgery (hallux valgus plasty).

### Patients and Methods

#### Patients

The following patients were eligible for admission to the study: patients of either gender, aged 18 to 75 years, hospitalised to undergo surgical treatment of hallux valgus, performed under local anaesthesia (foot block) or spinal anaesthesia, who gave their written informed consent to participate in the study. They were able to tolerate oral medication, complaining of postoperative pain rated as moderate or severe on a 5-point category scale (as none, slight, moderate, severe, very severe), occurring within 10 hours of the beginning of anaesthesia.

The following patients were not eligible for admission to the study: patients with known hypersensitivity or intolerance to paracetamol, with severely impaired hepatic function, with pain from an origin other than the local pain induced by the current surgery, with history of drug dependence or alcohol abuse, who had received any medication that might cause confusion in the interpretation of the efficacy or adverse effect liability of the study analgesics (all psychoactive drugs and analgesic drugs within 6 hours before administration of the study medication except for those defined by the anaesthesia protocol), and patients treated with NSAIDs, except if the treatment was discontinued at least 8 hours before administration of the study medications (24 hours for sustained-release formulations of NSAIDs).