Piritramide is a synthetic opioid that has been used for more than 30 yr in parts of Europe as the analgesic of choice for the management of postoperative pain. However, piritramide is not available in all countries and, as it is occasionally used in studies published in the *British Journal of Anaesthesia*, it seems pertinent to review its pharmacology.\(^1\)

The development of piritramide by Janssen Pharmaceutica was concurrent with that of fentanyl in 1960. It is a 4-amino piperidine derivative \((2,2\text{-}\text{diphenyl}\text{-}4\text{\{-4\text{-}carbamoyl\text{-}4\text{-}piperidino\}piperidine\}}\) butyronitrile) and has full mu receptor agonist activity.\(^2\) The presence of a piperidino ring gives it a unique and unusual structure for an opioid (Fig. 1).

![Fig 1 Chemical structure of piritramide.](image)

Lack of a suitable *in vitro* assay system for piritramide has limited the availability of human pharmacokinetic data. However, using a new gas chromatography technique,\(^3\) a recent study in healthy male volunteers has provided a pharmacokinetic profile.\(^4\) Mean volume of distribution at steady state concentrations \((V_{ss})\) was 4.7 (SD 0.7) litre kg\(^{-1}\); this is the largest reported \(V_{ss}\) of all opioids in clinical use, except for that of methadone (6.1 (2.4) litre kg\(^{-1}\)). Renal clearance was minimal (0.13 (0.09) ml min\(^{-1}\) kg\(^{-1}\)), with only 1.4% excreted unchanged. Total body clearance was 6.4–8.85 ml min\(^{-1}\) kg\(^{-1}\). This implies that elimination is almost entirely dependent on hepatic metabolism with an estimated extraction ratio of approximately 30% less than that of fentanyl.\(^5\) The nature of the metabolites of piritramide has not been determined.

After a bolus dose of piritramide 0.2 mg kg\(^{-1}\), the mean terminal elimination half-life was 478 (SD 85) min, more than twice that of morphine, fentanyl and pethidine. Increasingly, the context sensitive half-life \((T_{1/2}\text{context})\), that is the time for plasma concentrations to decrease by 50% after cessation of infusion,\(^6\) is being used as a more meaningful indicator of the duration of action of a drug than the elimination half-life after infusion. After a 30-min infusion, the \(T_{1/2}\text{context}\) of piritramide was approximately 3 h, considerably longer than that of alfentanil (0.4 h), fentanyl (0.7 h) or sufentanil (0.7 h).\(^7\) The equilibration half-life between plasma and the effect site was 16.8 (range 4.4–41.6) min, which is also longer than that of other opioids. It has been suggested that this is an advantage when the drug is given in intermittent i.v. bolus doses as the effect site is protected from rapid changes in concentration.\(^7\)

Both animal\(^2\) and human studies\(^8\) \(^9\) have demonstrated the morphine-like analgesic activity of piritramide, although data regarding analgesic potency are conflicting. Early studies described the clinical potency of piritramide as 0.7 of that of morphine.\(^10\)\(^\text{–}\)\(^12\) In contrast, some studies have demonstrated a slightly greater potency of piritramide compared with morphine.\(^8\) This inconsistency is probably related to study design (e.g. types of subjects and methods used to evaluate the analgesic response). However, it is likely that a dose of piritramide 15–20 mg i.m. can be expected to produce an analgesic action comparable with morphine 10–15 mg i.m.\(^10\)\(^\text{–}\)\(^13\) Early investigators suggested that piritramide may have potential advantages with respect to analgesic efficacy and side effects (i.e. long duration of action and low incidence of nausea and vomiting and respiratory depression\(^10\)\(^\text{–}\)\(^14\)) but this has not been confirmed by recent, well designed studies.

Despite a slow plasma–effect site equilibration half-time, a rapid onset of action has been reported: 2–4 min after i.v. injection and 0.5–1 h after i.m. injection.\(^8\)\(^\text{–}\)\(^9\) \(^12\) Duration of action is approximately 6 h.\(^7\)\(^\text{–}\)\(^9\)\(^\text{–}\)\(^12\) In a recent study, Albrecht and colleagues compared the effect of administering opioids just before termination of a remifentanil-based anaesthetic for major abdominal surgery. Only 55% of patients receiving piritramide required a second bolus of analgesia compared with 76% in the fentanyl group, 75% in the buprenorphine group and 79% in the morphine group. Median time from end of anaesthesia to requiring the second bolus was longer in the piritramide group (40 min) compared with the other groups (26–28 min).\(^15\)

During its development, it was claimed that piritramide was devoid of emetic effects. Furthermore, apomorphine-induced emesis was effectively blocked by low-dose piritramide in animal studies.\(^2\) Data from old clinical studies suggest that nausea and vomiting are rare side effects and an incidence of 0–3% has been reported.\(^8\)\(^\text{–}\)\(^9\)\(^\text{–}\)\(^12\)\(^\text{–}\)\(^16\) However, these data must be interpreted with caution as in some studies an antiemetic was administered,\(^12\)\(^\text{–}\)\(^16\) while in others no indication was given as to the use of antiemetic agents. There are no recent, well controlled studies to support these findings and comparative studies with other opioids are needed.

Respiratory depression has been reported with piritramide.
although it is not usually severe with therapeutic doses.\textsuperscript{9} \textsuperscript{12} \textsuperscript{17} Claims of a low potential for respiratory depression originate from early studies that examined ventilatory frequency and $P_{aCO_2}$ as indices of respiratory function. Weyne, Schluter and Lust\textsuperscript{9} and Delooz and Van de Walle\textsuperscript{18} demonstrated a lack of effect on these variables. In a study frequently quoted in support of the lack of a respiratory depressant effect of piritramide in comparison with morphine, Saarne demonstrated that an equipotent dose of morphine produced a greater increase in $P_{aCO_2}$, although this was not statistically significant.\textsuperscript{8} Other studies using spirometry and $P_{aCO_2}$ measurements indicated that equianalgic doses of piritramide and morphine produced similar effects.\textsuperscript{17} In a small comparative study with nalbuphine, piritramide caused significantly less respiratory depression.\textsuperscript{19} The respiratory depressant action of piritramide is reversible by naloxone.

Haemodynamic stability is well maintained at therapeutic doses\textsuperscript{8} \textsuperscript{9} \textsuperscript{12} although bradycardia and hypotension have been reported in some patients.\textsuperscript{20} Some investigators have studied the effect of piritramide on circulatory variables in patients undergoing cardiac surgery and demonstrated a significant reduction in peripheral vascular resistance similar to morphine.\textsuperscript{21} However, well controlled studies with invasive haemodynamic monitoring are lacking. Findings of cardiovascular stability in humans are in contrast with animal studies where cardiotoxicity with high dose i.v. piritramide has been reported.\textsuperscript{22} These have shown that the safety margin for cardiotoxicity was one-tenth that of morphine. In contrast with morphine, arrhythmogenic and negative chronotropic effects have been shown in \textit{ex vivo} animal studies.\textsuperscript{23}

The most common side effect of piritramide appears to be a dose-related incidence of sedation.\textsuperscript{8} \textsuperscript{10} \textsuperscript{16} \textsuperscript{20} It is reported in many studies, but rarely accurately quantified. Diaphoresis, urinary retention, flushing, focal myopathy and thrombophlebitis have all been reported.\textsuperscript{20} Piritramide is most commonly prescribed i.m. or i.v. for postoperative analgesia. It is used successfully for patient-controlled analgesia in adults\textsuperscript{14} and more recently in children.\textsuperscript{24} In this issue of the journal, Morlion and colleagues have examined the effect of a small bolus dose on the efficacy of postoperative patient-controlled analgesia using piritramide in a double-blind, randomized, controlled study.\textsuperscript{1} They have shown that reduction of the bolus size by 50\% from 1.5 mg to 0.75 mg resulted in a parallel reduction in opioid consumption but no difference between groups in terms of pain relief, side effects or patient satisfaction.

Piritramide remains a popular postoperative analgesic in Belgium, Germany, the Netherlands and Eastern Europe. Although there appears to be a lower incidence of reported emetic effects compared with morphine, these data are derived from indirect comparisons. Similarly, claims of a lower incidence of respiratory depression compared with morphine have not been clearly substantiated. Further well controlled studies are warranted to confirm any advantages of piritramide over morphine and other opioids.

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References

