Intravenous analgesic use in dialysis patients

Sir,

We would like to congratulate Dr Pauli-Magnus and his colleagues for their work that further elucidates the pharmacokinetics and hazards of the use of morphine in ESRD [1]. Opioids have been a mainstay of pain relief for centuries [2] (perhaps to the remotest period to which history extends) [3], yet they remain an essential part of our present day therapeutic armamentarium. More than 20 distinct alkaloids have been identified from opium and a variety of synthetic agonists and antagonists have been developed. However, when we performed a survey in February 1997, of 79 hospital-based pharmacies in the US, we found that the two most commonly prescribed intravenous analgesics for haemodialysis patients, morphine and meperidine, were the most noted for serious problems (Figure 1).

Morphine is primarily an agonist at the μ receptors with pain relief at μ, and respiratory depression and constipation resulting from agonist behaviour at μ, receptors [4]. Previous studies of morphine kinetics in renal failure have shown accumulation of morphine 6-glucuronide which has potent analgesic properties [5,6] and severe and prolonged respiratory depression [7] which has resulted in the mistaken diagnosis of cerebral damage in renal failure patients in intensive care [8], and unpredictable levels of sedation [9]. One group found that as little as 10 mg of morphine given intravenously produced sedation for 24 h, constricted pupils for 3 days and evidence of morphine metabolites 19 days after a single dose. Despite being placed on peritoneal dialysis within 36 h of the dose leaving them to conclude that any further use of morphine was no longer acceptable in patients with ESRD [10]. Dr Pauli-Magnus and his colleagues have added further concern by their work documenting the accumulation of morphine-3-glucuronide metabolite also [1].

Meperidine is a μ agonist similar to morphine. Dialysis patients demonstrate an accumulation of an active metabolite normeperidine [11], with a markedly prolonged half-life of 34.4 h that results in seizures and myoclonus [11,12] despite haemodialysis [11].

If morphine and meperidine are to be avoided, it appears that ketorolac was the most commonly cited drug in our national survey. Ketorolac, an intravenous NSAID, has the advantages of being a non-opiate analgesic. However, we found it to be the most common of the study drugs associated with complications. A low frequency of use undoubtedly contributed to such a high percentage of complications, yet the dialysis population has an inherent risk of gastrointestinal bleeding [13–15], and that appears to make ketorolac an unsuitable drug for this population since it has already been proven to be associated with increased incidence of gastrointestinal bleeding.

In contrast, in a retrospective chart review of 753 patients with ESRD who were followed at the Hypertension, Nephrology, Dialysis and Transplantation (HNDT) Clinic in Opelika, Alabama requiring hospitalization between January 1 1989 and March 1 1996, we found butorphanol to be the most frequently prescribed intravenous analgesic. Furthermore, we found no significant complications with butorphanol. Ketorolac was associated with 22% incidence of gastrointestinal bleeding and meperidine was associated with a 17% incidence of respiratory depression requiring a μ antagonist.

Butorphanol has previously been reported to be used with safety in children [16,17], with fewer complications than
Intravenous analgesics for haemodialysis for US hospitals.

2. Heberden W. "Dolor". In: T. Payne (ed.), Commentaries on the History and Cure of Diseases. Mews–Gate, London: 1802; was found to be the drug of choice in labour because of a lack of respiratory depression in the fetus [19]. Also, since it is a k agonist with the advantage of having less respiratory depression and less hypotension than morphine in dogs and normal subjects [20–24] with a ceiling effect of no further respiratory depression at high doses than at low doses [25]. Even deliberate attempts to produce respiratory failure have been unsuccessful. There is even one report of a 36-year-old man who injected himself with 100 mg of butorphanol along with 50 mg of detomidine, a central agonist designed to prolong the effect of butorphanol, in a suicide attempt [24]. Despite the massive doses, his respiratory rate never fell below 20 breaths/min and he never required mechanical ventilation. Likewise, in a more controlled study in dogs, even large (0.4 mg/kg) intravenous doses produced no changes in P CO₂ [26]. As a result, butorphanol has found to be safely given traumatic shock [27] and septic shock [28]. Furthermore, because it is a partial agonist at the m receptor, butorphanol has been used to reverse the respiratory depression of morphine and oxymorphone [29–31], and since it has no agonist properties at the m receptor, unlike buprenorphine, 4 mg of butorphanol is easily reversed by 0.3 mg of naloxone [20]. Additionally its major metabolite, hydroxybutorphanol, is thought to be clinically inactive [32–34], providing further safety in dialysis patients. Finally, the fact that butorphanol (but not morphine) has been found to actually improve nutrition in uraemic subjects [35] would seem to make it an ideal choice for intravenous analgesia in ESRD where poor nutrition is a marker of high mortality. We found it to be used with great safety and therefore butorphanol pharmacokinetics should be further evaluated in ESRD since it may become the intravenous analgesic of choice.

Hypertension, Nephrology, Dialysis and Transplantation Clinic

Charles J. Diskin, Selby Thomas

Auburn University

Opelika, AL

US


