

PENICILLIN (Commentary)

Speed of administration

Benzylpenicillin is an extremely nontoxic drug (if the risk of hypersensitivity developing in response to previous exposure is discounted). It is, however, known that it can be epileptogenic when CSF levels exceed 10 mg/l, and that penicillin is much more neurotoxic than any of the other related beta-lactam antibiotics. An intrathecal injection can also cause the patient to become drowsy and hyperreflexic. Hallucinations have been described, while coma and death have occurred when levels are exceedingly high. (See the review by Schliamser in 1991 for a discussion of these issues.) Such problems are **very** rarely encountered with IV administration because CSF penetration is poor even in patients with meningitis (~5% of plasma levels). However, toxicity does still occur occasionally when repeated large doses are given to patients in severe renal failure despite the fact that the drug is known to be almost entirely eliminated by the kidney. The main factor known to precipitate neurotoxicity with high dose treatment is some disturbance to the blood-brain barrier – the commonest causes being an intracranial tumour, cranial irradiation and microembolic damage during cardiac surgery. These findings account for the advice that direct intrathecal treatment is unwise, and that the dosage level must be halved when there is severe renal failure.

The findings do not, however, explain why almost all reference texts say that high IV doses, of the type recommended in the neonatal period (especially where group B streptococcal meningitis is a possibility), must be given slowly. The advice almost certainly stems from a statement in the manufacturer's Data Sheet (SPC) that adult doses in excess of 1.2 g should be given at a rate not exceeding 300 mg/min "to avoid high levels causing irritation to the central nervous system". Such advice is almost certainly generated by a misplaced concern that even transient high plasma levels will be translated into high CSF levels. The recommendation persists, nevertheless, and gets copied uncritically from text to text despite the lack of any reports of rapid administration causing any trouble. Similar, legally-inspired, long-discounted, concern for ototoxicity underpins the recommendation that all aminoglycosides should also be infused slowly over a 30 minute period when given IV in North America – a recommendation that has no counterpart in the advice the companies give when marketing the same products in Europe. More recently advice has begun to appear in the UK to the effect that fluxcloxacillin has to be given slowly over 30–60 minutes (*BNF for children*, 2005), but the evidence for this advice seems to be equally unlocatable.

Manufacturers offer similar advice in respect of a range of other antibiotics and, on inquiry, it often transpires that this is merely because that was how the product was first administered experimentally while under development. Were all such advice to be followed scrupulously it would greatly increase the work of nursing staff, leaving them with even less time to complete their many other duties and responsibilities. In fact many tens of thousands of rapid antibiotic injections have been given IV to small children over the years without a single adverse reaction ever being reported. Rapid delivery has become an inevitable consequence of the move towards giving almost all parenteral medication IV in the last 20 years – a strategy that nurses, in particular, see as a way of minimising the pain associated with IM injections. Rapid administration is unavoidable when a drug has to be given through a 'stopped off' IV cannula left in place specifically to make such treatment possible, and years of experience testify to the safety of this approach when giving a wide range of drugs.

That no problem has ever been recognised does not of course, of itself, mean that rapid bolus injection should be employed when an alternative exists. It is, however, perfectly possible to give any small volume (< 2 ml) injection to a small baby IV without setting up a separate line and syringe pump by following the advice given in the introduction to this *Formulary* as long as there is an IV infusion already running. A 60 mg/kg IV dose of benzylpenicillin when so given will not usually be infused at a rate that exceeds 6 mg/kg.min (the equivalent of a rate of 300 mg/min in a 50 kg adult). Mechanical infusion pumps need, of course, be used whenever a slow, controlled or continuous infusion is required, as Roberts was the first to recognise (Roberts, 1981). For all the products mentioned in this *Formulary* where such a need exists specific advice to this effect is given in the relevant monograph.

References

- Fossieck B, Parker RH. Neurotoxicity during intravenous infusion of penicillin. A Review. *J Clin Pharmacol* 1974;**14**:504-12.
- Roberts RJ. Intravenous administration of medication in pediatric patients: problems and solutions. *Pediatr Clin North Amer* 1981;**28**:23-34.
- Schliamser SE, Cars O, Norrby SR. Neurotoxicity of β -lactam antibiotics: predisposing factors and pathogenesis. *J Antimicrob Chemother* 1991;**27**:405-25.