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STUDIES ON INTRAVENOUS PARACETAMOL: AN OVERVIEW

Jitendra Rajak

Principal, S.M.D. College, Punpun, Patna.

ABSTRACT

A Fatal Accident Inquiry in Scotland in 2011 concluded that a young adult died from liver failure due to an overdose of paracetamol. The Sheriff found 'there was, at the time of the death, a prevailing culture of assumed familiarity with the administration of IV paracetamol, a familiarity derived from the common use of oral paracetamol'. The patient, who weighed 35kg, died nine days after receiving paracetamol 1g IV on a sustained and regular basis.¹

KEYWORDS- Fatal Accident Inquiry, oral paracetamol, drug prescription.

INTRODUCTION :

Intravenous paracetamol was licensed in the UK in 2004 and is used routinely in anaesthetic practice. Since introduction, there have been concerns about accidental overdose of IV paracetamol due to errors in drug prescription and administration, particularly in children, small adults, the elderly, alcoholics and those with pre-existing hepatocellular insufficiency.



Reported errors include incorrect dose in adults with high or low body mass index; accidental overdose in children associated with use of 100ml-vials; 10-fold drug calculation errors; confusion between dose volume in millilitres and dose of drug in milligrams; errors when setting up infusion pumps; and duplication of doses between the ward and the operating theatre or recovery.²⁻⁵

Examples of recent reports to the NRLS include:

- Patient had a dose of paracetamol before going to theatre and then was given another dose whilst in theatre. Fifth dose in 24 hours.
- Paracetamol not given on the ward post op due to double dose given in theatre...
- Patient was given the prescribed 1gram paracetamol on the ward at 08:13hrs as part of pre-med. On return to ward after procedure it was noted on the anaesthetic chart that 1gram of IV paracetamol had been given at 09:30 hrs...

The MHRA issued a Patient Safety Update in 2010 that raised concerns about accidental overdose of IV paracetamol (Perfalgan®), especially in infants and neonates. Perfalgan® is presented in a concentration of 10mg/ml, and in most cases, a 10-fold overdose was reported. The MHRA advised vigilance when prescribing and administering Perfalgan®, to adhere to recommended doses and dose intervals, to avoid concomitant administration by different routes, and to use 50ml vials for infants and children who weighed less than 33kg.³

The NPSA issued a Signal alert in 2010 that raised concern about the risk of inadvertent overdose of IV paracetamol in children, and described 206 incidents relating to IV paracetamol, two associated with severe harm and 14 with moderate harm.⁵

Recommended dose of IV paracetamol

The dose of IV paracetamol recommended

by the MHRA for children and adults is shown in the table below. Paracetamol should be given by infusion over 15 minutes, and the minimum dose interval should not be less than four hours (six hours in patients with renal impairment).

	Term newborn infants, infants, toddlers and children weighing <10kg*	Children weighing >10kg and <33kg	Children, adolescents, and adults weighing >33kg and <50kg	Adolescents and adults weighing >50kg
Dose of IV paracetamol (per infusion administration)	7.5mg/kg	15mg/kg	15mg/kg	1g
Maximum daily infusion dose**	30mg/kg	60mg/kg	60mg/kg	Must not exceed 4g

*The dose of IV paracetamol is controversial in neonates and infants. The BNF for Children (BNFC) suggests a dose of 7.5mg/kg every 8 hours (maximum 25mg/kg daily) in preterm neonates over 32 weeks postmenstrual age, 10mg/kg every 4-6 hours (maximum 30mg/kg daily) in neonates.⁶

**The British National Formulary (BNF) suggests caution in patients with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition or dehydration, and to administer a maximum daily infusion dose of 3g in adults in these patient groups.⁶

TREATMENT OF IV PARACETAMOL OVERDOSE

Paracetamol is metabolised in the liver by glucuronidation and sulphation; a small proportion is metabolised by oxidation to toxic metabolites such as N-acetyl-p-benzoquinone-imine. Benzoquinoneimine is combined with glutathione and is excreted safely in the urine, but if glutathione stores are depleted, benzoquinoneimine accumulates and potentially fatal hepatic damage may occur.

Patients in the peri-operative period may be particularly vulnerable to the toxic effects of paracetamol as it may be administered regularly over a number of days, and patients may have low glutathione levels due to starvation or preexisting nutritional deficiency.^{7,8}

The treatment for paracetamol toxicity is IV infusion of acetylcysteine, which restores the ability of the liver to produce glutathione. Nomograms for the treatment of paracetamol toxicity are based on time since ingestion of oral paracetamol and the plasma level at four hours. Overdose with IV paracetamol poses a specific management problem, as standard nomograms cannot be directly applied. In IV paracetamol overdose plasma levels peak immediately after IV injection, and will normally be lower than predicted from the same oral dose at the same time after ingestion.

Guidance on management of IV paracetamol overdose is available from the UK National Poisons Information Service (NPIS), and guidance is updated regularly on Toxbase, the database of the NPIS (<http://www.toxbase.org>). IV paracetamol is potentially very toxic in overdose and managing clinicians are encouraged to discuss all patients with overdose with the local poisons information service (UK NPIS, in Ireland, National Poisons Information Centre www.poisons.ie).

Currently the NPIS advises acetylcysteine administration following a single intravenous dose of paracetamol above 60mg/kg. Do not wait for the result of the plasma paracetamol concentration. For pregnant patients, the toxic dose should be calculated from the pre-pregnancy weight; for patients above 110kg, the toxic dose should be calculated from a maximum weight of 110kg.

If the dose of IV paracetamol administered is unknown or uncertain, the treatment nomogram should be used to obtain an estimate of risk based on a blood sample taken four hours after dosing. Treatment should be initiated if plasma paracetamol is >50mg/l at four hours (i.e. half the value of the four hour plasma concentration in oral overdose).² Patients who present late, or with multiple doses of IV paracetamol exceeding 60mg/kg in 24 hours should be treated with acetylcysteine. Neonates are particularly susceptible to IV paracetamol overdose

and treatment with acetylcysteine should be considered in all overdoses.

CONCLUSION

Intravenous paracetamol is a relatively new preparation, and is under close scrutiny by the MHRA and internationally; it is recommended that all cases of adverse reaction to IV paracetamol are reported to the MHRA 3,4,9 and all cases of IV paracetamol overdose are discussed with the NPIS/NPIC so that experience of these cases can be collected.

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