COURSE CODE:
PAMA11003

ASSIGNMENT #2-Short Answer Questions:

Perfalgan®

“Paracetamol Solution for Infusion”

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**INTRODUCTION**

Perfalgan® described as “paracetamol solution for infusion” contains the active ingredient paracetamol, which is an effective medication for mild to moderate pain, and is also widely used as an antipyretic agent. Paracetamol is available for administration by oral, rectal and most recently, by the intravenous (IV) routes. The purpose of this paper is brief pharmacological review of Perfalgan® as an IV-administered analgesic agent.

**INTRAVENOUS PARACETAMOL**

**Why do we need a solution of this particular active ingredient?**

A solution of paracetamol (as active ingredient of Perfalgan®) simply can be administered intravenously (IV). Although the easiest and cheapest method of administration is oral, however, that is not an option intra-operatively or in some patients (e.g. patients with bowel obstruction). The rectal form of administration is unreliable and erratic, and gives a very variable peak plasma concentration, which is also reached later, at 2 to 3 hours. As with most drugs, IV administration is more reliable and reaches peak concentrations faster compared to oral routes, as proven for paracetamol [1]. Another issue is side effects of paracetamol. Since its side effect profile is considerably superior, availability of an IV form is very useful when other routes are less feasible [2].

**Is the active ingredient naturally water-soluble?**

No, the active ingredient (i.e. paracetamol) is not water-soluble naturally. Hydrophilic ingredients in Perfalgan like mannitol and disodium phosphate make it soluble [2].

**Is it a chiral molecule?**

The following diagrams show structural formula of paracetamol that consists of a benzene ring attached by a hydroxyl group on one side and an amide group on the other side.
As it is obvious in structural formula, paracetamol has no chiral carbon, and therefore it cannot have any optical (i.e. chiral) isomer.

**How does paracetamol differ to propacetamol?**

Propacetamol is a pro-drug form of paracetamol, and is formed from esterification of paracetamol, and the carboxylic acid diethylglycine. Compared to paracetamol it is more water soluble and rapidly hydrolysed (7 minutes after administration) by plasma esterases. Since propacetamol requires reconstitution, it can cause contact dermatitis in healthcare professionals (e.g. nurses) who handle the drug [3]. In addition it causes pain at the site of injection. Perfalgan®, which is presented as a ready-to-use solution, does not require reconstitution. No incidences of contact dermatitis have been reported, nor have there been reports of its infusion causing discomfort [4-6].

**PHARMACOKINETICS**

**What is the expected time course of action?**

The time course of action is quick with Perfalgan®. According to product information sheet it takes about 15 minutes to reach maximum plasma concentration (i.e. as soon as infusion is complete), and it provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in one hour and duration of this effect is usually 4-6 hours. Plasma half-life is 2.7 hours and total body clearance is 18 L/h.

**Can the time course of action be altered?**

Yes, it can be altered by speed of infusion and volume of distribution (Vd). If the speed of infusion is slowed down, then the onset and time to peak effect will be prolonged, and if the patient is very heavy or large, the peak effect may be decreased (higher Vd and hence lower peak plasma levels) [2].

**Why is the bioavailability from 500 mg Perfalgan® said to be the same as that from 1 g propacetamol? How is this determined?**

Propacetamol is formed from esterification of paracetamol, and the carboxylic acid diethylglycine, a dose of 1 g of propacetamol yields to 500 mg of paracetamol after
hydrolysis by plasma esterases. Therefore, it can be concluded that the ratio of 1:1 applies by default. Conversely, active ingredient of 500 mg Perfalgan® is 500 mg of paracetamol as a ready-to-use solution.

**METABOLISM**

*Does Perfalgan® have active metabolites? How are they active?*

Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. These primary metabolites, which account for about 90% of the dose excreted, are remarkably safe compounds [9]. A small fraction (less than 4%) is metabolised by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, during massive poisoning, the quantity of this hepatotoxic metabolite is increased. As the dose of paracetamol increases, the quantity of benzoquinone imine produced increases too. There then comes a point where the glutathione stores in the liver have been completely used up and the rate of production of new glutathione cannot keep up with the rate of production of the benzoquinone imine. At this point benzoquinone imine attaches to liver protein and causes liver injury [9].

**MECHANISM OF ACTION**

*What is the mechanism of action of Perfalgan®?*

As with many other medications, the effectiveness of paracetamol was discovered without knowing how it works. Despite the popularity of this pain reliever, the mechanism by which achieves its analgesic and anti-pyretic effects is still debated, and the subject of continuing research.

Analgesic and anti-inflammatory effects of non-steroidal anti-inflammatory drugs (NSAIDs) are thought to relate to their inhibition of the cyclooxygenase enzymes (COX-1 and COX-2), which leads to inhibition of prostaglandin (PG) production. Unlike NSAIDs paracetamol has no significant action on COX-1 and COX-2 [8]. This explains lack of anti-inflammatory action of paracetamol and also, more importantly, absence of typical
NSAIDs-related side effects, namely gastrointestinal problems. Chandrasekharan et al (2002) described COX-3 as third COX iso-enzyme (distinct from COX-1 and COX-2) mediating analgesia in humans [10]. However, subsequent research has suggested lack of active COX-3 in humans, and therefore improbability of its role in PG-related analgesia and anti-pyrexia [11]. Recent research has suggested a central mechanism of action for paracetamol. This central analgesic effect is mediated through activation of descending serotonergic pathways [12]. There are other mechanisms of action proposed including inhibition of the L-arginine-nitric oxide (NO) pathway mediated through substance P or N-methyl-D-aspartate (NMDA), and active paracetamol metabolites that have effect on cannabinoid (CB) receptors [13-15].

**EFFECTIVENESS IN TREATMENT OF ACUTE PAIN**

**Is Perfalgan® useful in the treatment of acute pain? On what evidence?**

There is good evidence to show paracetamol as an effective and safe analgesic for treatment of acute pain. The best evidence is its usefulness in treatment of acute postoperative pain. The efficacy of single-dose paracetamol as a postoperative analgesic has been confirmed by various studies [16]. Paracetamol is therefore an effective postoperative analgesic [17-18], with potency slightly less than a standard dose of morphine or the NSAIDs [19-20].

**PRECAUTIONS AND SIDE EFFECTS**

**What precautions should be observed for use of Perfalgan®?**

Since paracetamol is metabolized in liver, it should be used with caution in cases of hepatic disorders. Patient with hepatocellular insufficiency, viral hepatitis, chronic alcoholism, and excessive alcohol intake (3 or more alcoholic drinks every day) [21] are at risk for paracetamol-induced hepatotoxicity since glucuronide conjugation of the drug may be decreased.

Paracetamol should be used cautiously in patients with renal insufficiency (creatinine clearance ≤ 30 mL/min). Nephrotoxicity is less common than hepatotoxicity in paracetamol overdose but renal tubular damage and acute renal failure occur even in the absence of hepatotoxicity [22].
It is also contraindicated for patients with G6PD-deficiency, chronic malnutrition, and some alcohol abusers, who have low reserves of glutathione to counteract the N-acetyl-p-benzoquinone-imine produced [2]. It can cause hemolytic anemia in G6PD-deficiency cases.

Are the side effects problematic? Side effects of paracetamol, taken at recommended doses, are mild to non-existent [23], and only higher than recommended doses can cause problematic side effects (i.e. hepatotoxicity and nephrotoxicity). The rare side effects can include skin hypersensitivity (rash), hypotension, and blood disorders, such as thrombocytopenia and leukopenia.

**Total count of words: 1280**

**References:**


   At: http://www.pharmweb.net/pwmirror/pwy/paracetamol/pharmwebpic.html


