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Acetaminophen with Combination of Essential Amino Acids: A Review with Respect to Military Conflicts Region of World

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Abstract

Paracetamol (acetaminophen or para-hydroxyacetanilide) is a non-opioid analgesic and antipyretic agent used to treat fever and mild to moderate pain [1-3]. It is a widely used over the counter medication and common brand names include Tylenol and Panadol. At present there are many military conflicts going on in word. So peoples around these areas need to be very cautions regarding their health. As soon as any wound observed 1st medicine prescribed to avoid pain, inflammation is paracetamol. Also in these areas due to heavy military conflicts malnutrition observed in all peoples.

Although overdose of paracetamol is very rare in occurrence in other part of word due to its last metabolite which damages the liver, but in these military conflicts areas there are no such monitoring for local bodies, government or by any international bodies. So there must be a chance of occurrence and reoccurrence of paracetamol poisoning in these areas. To avoid such incidents and safety of peoples there is a proposed combination of paracetamol with amino acids such as methionine and cysteine. Although this combination is well known and used from late 80's but now time has change.

Keywords: Acetaminophen; Amino Acid; Metabolism; Derivative

History

Paracetamol (acetaminophen, N-acetyl-p-aminophenol) is one of the most widely used over-the-counter analgesic antipyretic drugs. It was first synthesized by Joseph von Mering in (1893) by reacting p-nitrophenol with tin and glacial acetic acid.

Paracetamol poisoning, also known as acetaminophen poisoning, is caused by excessive use of the medication paracetamol (acetaminophen) [4]. Most people have few or non-specific symptoms in the first 24 hours following overdose. These symptoms include feeling tired, abdominal pain, or nausea. This is typically followed by absence of symptoms for a couple of days, after which yellowish skin, blood clotting problems, and confusion occurs as a result of liver failure. Additional complications may include kidney failure, pancreatitis, low blood sugar, and lactic acidosis. If death does not occur, people tend to recover fully over a couple of weeks [5,6]. Without treatment, death from toxicity occurs 4 to 18 days later [5].

At therapeutic doses, APAP is metabolized via glucuronidation and sulfuration reactions occurring primarily in the liver and results in water-soluble metabolites that are excreted renally. As a result of the metabolic conversion of APAP by the microsomal CYP-450 enzyme system, a highly reactive intermediate, N-acetyl-p-benzoquino- neimine (NAPQI), is produced [6]. NAPQI directly reacts with glutathione (GSH), and at overdoses of APAP, the depletion of cellular GSH occurs. This allows NAPQI to bind to cellular proteins and initiate lipid peroxidation, leading to hepatic [6] and renal [7] injury.

Acetaminophen with Amino Acids

There have been no reports of overdose with paracetamol and methionine combinations in humans and therefore no hard evidence exists that liver damage would be prevented. Nevertheless, adding methionine to paracetamol tablets to prevent hepatic damage from overdose has a sound biochemical rationale.

Excessive production of N-acetyl-p-benzoquinoneimine, a toxic metabolite of paracetamol, depletes hepatic glutathione concentrations leading to covalent binding and destruction of hepatic cells. Methionine protected against such damage in animal studies [8,9] and in clinical trials (when given to patients who admitted taking a paracetamol overdose) [10-13]. It probably acts by promoting synthesis of glutathione.

Methionine is an essential amino acid present in dietary meat (approximately 2 g per day) and it has been co-formulated with some paracetamol tablets in the UK (formerly Pameton, with 300 mg methionine in each tablet, SmithKline Beecham and currently Paradote, with 100 mg methionine in each tablet, Penn Pharmaceuticals).The advantage of such a combination tablet is that methionine is a substrate for glutathione synthesis.Therefore, in the event of a paracetamol overdose, it acts as an antidote and the levels of glutathione would be expected to be high enough to prevent significant tissue damage from occurring [14].However, potential safety issues concerning methionine supplementation have been identified (Table 1) [14]. A recent study shows that moderate methionine loading at the amount present in combination paracetamol/methionine tablets may not in fact raise homocysteine levels significantly, for cardiovascular problems to occur [15]. At high doses, methionine causes nausea, headache, vomiting, drowsiness, and irritability [14].

Table 1: Potential risks of methionine

Risk Group	Reasons	Reference
Pregnant women	Methionine is metabolised to homocysteine and raised plasma homocysteine is associated with birth defects, pre-eclampsia, spontaneous abortion and placental abruption.	15, 16
Schizophrenic patients	Schizophrenic patients given 10–20 g methionine daily developed functional psychoses.	17
Patients with pre-existing cancer	Animal studies have shown that restriction of methionine intake blocks division and metastasis of tumour cells.	18,19
Ischaemic heart disease (IHD), peripheral vascular disease (PVD), stroke	Methionine is metabolised to homocysteine – raised homocysteine levels are associated with IHD, PVD and stroke.	20-22
Patients with chronic liver disease	The liver has an impaired ability to metabolise methionine.	22

Discussion

Paracetamol poisoning can occur accidentally or as an attempt to die by suicide. Risk factors for toxicity include alcoholism, malnutrition, and the taking of certain other hepatotoxic medications [23]. Liver damage results not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinone imine (NAPQI) [24]. -NAPQI decreases the liver's glutathione and directly damages cells in the liver [25]. Diagnosis is based on the blood level of paracetamol at specific times after the medication was taken [23]. These values are often plotted on the Rumack-Matthew nomogram to determine level of concern [23].

Treatment may include activated charcoal if the person seeks medical help soon after the overdose [23]. Attempting to force the person to vomit is not recommended [24]. If there is a potential for toxicity, the antidote acetylcysteine is recommended [23]. The medication is generally given for at least 24 hours [24]. Psychiatric care may be required following recovery [23]. A liver transplant may be required if damage to the liver becomes severe. The need for transplant is often based on low blood pH, high blood lactate, poor blood clotting, or significant hepatic encephalopathy. With early treatment liver failure is rare [24]. Death occurs in about 0.1% of cases [23].

One strategy for reducing harm done by acetaminophen overdoses is selling paracetamol pre-combined in tablets either with an emetic [26] or an antidote. Paradote was a tablet sold in the UK which combined 500 mg paracetamol with 100 mg methionine [27], an amino acid formerly [28] used in the treatment of paracetamol overdose. There have been no studies so far on the effectiveness of paracetamol when given in combination with its most commonly used antidote, acetylcysteine [29,30].

Conclusion

There is still no solid report find in reference that whether to use methionine in combination with paracetamol or not. But there are many reference available that this avoid paracetamol poisoning. Also amino acid nutrient fulfilled if use with amino acid. Although current review report is not specific for military conflicts affected peoples but it is also useful for common peoples. There is still lots of scope in this combination in future.

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