Case Report

Accidental Acute Poisoning of two Children by Paracetamol-Codeine (1000 Mg/60 Mg) Association - A Case Report

Abstract

Paracetamol is one of the most used drugs in the world [1]. It’s also one of the most common drugs that children accidentally ingest. Unlike the situation in adults, death and hepatotoxicity in children from paracetamol poisoning are exceedingly uncommon events [2]. After ingestion it is rapidly and completely absorbed from the gastrointestinal tract. Approximately 85-95% of the absorbed paracetamol is metabolized by the liver and excreted in the urine as nontoxic metabolites. About 5 to 15% of paracetamol ingested is metabolized by cytochromes P-450 in toxic metabolite. N-acetyl para-quinoneimine, a very toxic compound, which is detoxified by glutathione present in the liver with glutathione S - transferase. In para-quinoneimine, a very toxic compound, which is detoxified by glutathione S - transferase. In massive intoxication with paracetamol, glutathione detoxification capacity is exceeded. This leads to hepatocellular necrosis with the release of liver enzymes in the blood [3]. Paracetamol is a major cause of fulminant hepatitis [4], occurring 24 to 48 hours after the onset of poisoning.

But codeine is a morphinomimetic produced after the metabolism of morphine [5]. It is used in the treatment of pain. Unlike paracetamol poisoning, poisoning by an association of paracetamol and codeine are not well documented, especially those of children. Poisoning, poisoning by an association of paracetamol and codeine (1000 mg/60 mg) rectal suppository, instead of the child 1 (2 years old) has received one rectal suppository in the morning and one in the evening for 2 days that is to say 154 mg/kg of paracetamol and 9 mg/kg of codeine per day.

A persistent fever (39°C), associated to an asthenia, vomiting, sweating and especially abdominal pain is identified on the child 1 during the examination. There was also an abdominal guarding during palpation of the abdomen. The results of laboratory tests have shown an increase in transaminases (ALT = 2179 IU / L, AST = 1800 IU / L), γ-glutamyl transferase (GGT = 109 IU / L); microcytic hypochromic anaemia with normal sedimentation rate and negative Widal serodiagnosis (Table 1). Alkaline phosphatase was slightly elevated indicating a cholestasis associated with a hepatotoxicity. The toxicological analysis of urine by thin layer chromatography (TLC) has showed the presence of paracetamol. Because of the lack of material for the realization of toxicological analysis the paracetamol levels in the blood were not done. The analysis of feces was normal.

The treatment of the intoxication has consisted initially in a release of all the drugs and an administration of metamizole and N-acetylcysteine. The dose of N-acetylcysteine administered orally, is 140 mg/kg followed by 70 mg/kg every 4 hours for 10 days. After one week of treatment, abdominal pains have disappeared. After 10 days transaminases and GGT were back to normal.

Unlike the child 1, the child 2 (3 years old/13 kg) has received 3-year old were suffering from malaria. After a consultation in the Medical Center of the Police of Lomé (Togo), paracetamol rectal suppository was prescribed. Unfortunately the pharmacies have delivered the adult form of paracetamol-codeine (1000 mg paracetamol and 60 mg codeine) rectal suppository, instead of the child form.

Apart from other prescribed drugs like antimalarial and antibiotic, the child 1 (2 years old) has received one rectal suppository in the morning and one in the evening for 2 days that is to say 154 mg/kg of paracetamol and 9 mg/kg of codeine per day.

Observation

Both intoxicated children, the first 2 years old and the second

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Table 1: Biochemical and hematological parameters of Child 1 on day 1 and day 10 after an accidental acute poisoning by a paracetamol-codeine (1000 mg/60 mg) association.

| Parameters                          | Day 1 | Day 10 | Reference ranges |
|-------------------------------------|-------|--------|------------------|
| AST (U/L)                            | 2179  | 53     | M: ≤ 38 U/L      |
| ALT (U/L)                            | 1800  | 53     | F: 31 ≤ U/L      |
| GGT (U/L)                            | 109   | 82     | M: ≤ 51-50 U/L   |
| Alkaline phosphatase (U/L)           | 420   | 382    | F: 7-32 ≤ U/L    |
| Haemoglobin (g/dL)                   | 11    | 11     | 12 – 14 g/dL     |
| Haematocrit (%)                     | 35.2  | 35     | 38 – 44 %        |
| MCV (fl)                             | 70    | 71     | 74 – 88 fl       |
| MCH (pg)                             | 21.9  | 22     | 27 – 31 pg       |
| MCHC (%)                             | 31.3  | 32     | 32 – 36 g/dl     |
| WBC (10³/µL)                         | 9300  | 8000   | 5000 – 13 000 /mm3|
| Platelet (10³/µL)                    | 325 000 | 400 000 | 150 000 – 450 000 /mm3 |
| ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase and GGT: Gamma Glutamyl Transpeptidase. |

Table 2: Biochemical and hematological parameters of Child 2 on day 1 and day 3 after an accidental acute poisoning by a paracetamol-codeine (1000 mg/60 mg) association.

| Parameters                          | Day 1  | Day 3  | Reference ranges |
|-------------------------------------|--------|--------|------------------|
| AST (U/L)                            | 29     | 27     | M: ≤ 38 U/L      |
| ALT (U/L)                            | 15     | 15     | F: 31 ≤ U/L      |
| GGT (U/L)                            | 30     | 20     | M: ≤ 51-50 U/L   |
| Alkaline phosphatase (U/L)           | 421    | 534    | F: 7-32 ≤ U/L    |
| Haemoglobin (g/dL)                   | 7.5    | 7.1    | 12 – 14 g/dL     |
| Haematocrit (%)                     | 25.10  | 23.6   | 38 – 44 %        |
| MCV (fl)                             | 72.50  | 72     | 74 – 88 fl       |
| MCH (pg)                             | 21.70  | 21.6   | 27 – 31 pg       |
| MCHC (%)                             | 29.90  | 30.1   | 32 – 36 g/dl     |
| WBC (10³/µL)                         | 8500   | 5000   | 5000 – 13 000 /mm3|
| Platelet (10³/µL)                    | 105 000| 211 000| 150 000 – 450 000 /mm3 |
| ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase and GGT: Gamma Glutamyl Transpeptidase. |

The rectal suppository discontinuously for several days, once a day or once every 2 days. After three weeks of treatment with the suppository (and other drugs like antimalarial and antibiotic), the persistence of anaemia may not be related to the paracetamol poisoning, because anaemia is endemic in Africa due to malaria [6,7].

Discussion

Normal therapeutic dose of paracetamol is 60 mg/kg for adults and 20 to 50 mg/kg for children. Severe poisoning in children manifests that above 150 mg/kg [3]. Child 2 (3 years old/13 kg) who has received high doses of paracetamol and codeine discontinuously was apparently not severely intoxicated. Poisoning of the 2 children although due to a combination of two active ingredients, paracetamol and codeine, only the toxic effect of paracetamol was observed. Other drugs used for the treatment of malaria (arthemether) and anaemia (iron and vitamins) are used correctly and are not responsible of liver poisoning. The paracetamol poisoning is manifested by the increase of child 1’ liver enzymes (transaminases, GGT) and abdominal pain. A discrete cholestasis associated with a hepatic cytolyis is observed in relation to the increase in alkaline phosphatase. The presence of anaemia may not be related to the paracetamol poisoning, because anaemia is endemic in Africa due to malaria [6,7].

The toxic effects of codeine (toxic threshold: 2mg/kg), such as depression of the central nervous system (CNS) have not been observed during these intoxications however the two children had a marked lethargy and fatigue. Pancreatitis reported during poisoning by paracetamol-codeine combination was not observed [8,9]. Amylases were not assayed.

The unavailability of the injectable form of the N-acetylcysteine has led us to use the oral form, available in pharmacies to treat coughs. The oral route is also the practice in USA [10]. Wallace and his team published the only evidence-based flowchart in 2002 and was accepted by the Royal College of Paediatrics and Child Health as a Good Practice Consensus Statement. The dose is 150 mg/kg in 3 ml/kg of 5% dextrose over 15 minutes, followed by 50 mg/kg in 7 ml/kg 5% dextrose over 4 hours followed by 100 mg/kg in 14 ml/kg 5% dextrose over 16 hours. For continuation of NAC as adjuvant therapy for hepatic failure, it should be given at 150 mg/kg per 24 hours [11].

Topics malnourished or those with glutathione depletion have a higher risk to paracetamol poisoning than others [12]. In these subjects at risk it is recommended to administer NAC even when the serum level in paracetamol is below the values considered toxic [12].

Conclusion

Errors in drug delivery may be responsible for serious accidents especially for children. In the case of paracetamol overdose, the toxic hepatitis can be serious. It may follow as in the present case, cholestasis characterized by increases in alkaline phosphatase. The administration of paracetamol antidote proved very beneficial as...
levels of liver enzymes in the blood have returned to normal values.

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