EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Section 4.9: Overdose

SmPC training presentation

Note: for full information refer to the European Commission's Guideline on summary of product characteristics (SmPC)

SmPC Advisory Group

Index

I. General objectives of section 4.9

This section should provide relevant information to:

- Detect an overdose, and
- Ensure the appropriate management

II. Key principles

Describe

1. Acute symptoms and signs and potential sequelae
2. Management of overdose
   - Monitoring
   - Use of agonist/antagonist/antidote
   - Method to increase elimination

Any dosage recommendation of other medicinal products (e.g. antidotes) should usually not be mentioned

Examples

1 symptoms & management
2 symptoms & management
3 symptoms & management
4 symptoms & management

Special Populations

Provide information specifically observed in special populations such as elderly, patients with renal impairment or hepatic impairment, other concomitant diseases etc

5 special populations

Paediatric Population

Special mention should be made of those medicinal products/strength of formulation for which ingestion of only one dose unit by children can cause fatal poisoning

6 Paediatric
7 Paediatric

Example 1-symptoms & management

Describe acute symptoms and signs and potential sequelae and management of overdose in man

Active substance X 20 mg coated tablets

4.9 Overdose

Signs and symptoms

Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral active substance X.

Management of overdose

There is no specific antidote for active substance X. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of active substance X by 50 to 60%. Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

Example 2-symptoms & management

Describe acute symptoms and signs and potential sequelae and management of overdose in man

Active substance X 2 mg/ml solution for injection

4.9 Overdose

Frequently observed symptoms of overdose are nausea, vomiting, diarrhoea, severe bone marrow depression (including anaemia, thrombocytopenia, leukopenia, and agranulocytosis), acute renal insufficiency, as well as irreversible neurologic toxicity (paraparesis/quadriparesis), Guillain-Barré syndrome, and Brown-Séquard syndrome. Acute, irreversible neuro- and nephrotoxicity have been described in individual patients treated at a dose which was ≥ 4 times higher than the recommended regimen for hairy cell leukaemia.

No specific antidote exists. Immediate discontinuation of therapy, careful observation, and initiation of appropriate supportive measures (blood transfusions, dialysis, haemofiltration, anti-infectious therapy, etc.) are the indicated treatment of overdose of active substance X. Patients who have received an overdose of active substance X should be monitored haematologically for at least four weeks

Example 3-symptoms & management

Describe acute symptoms and signs and potential sequelae and management of overdose in man

Active substance X 50 micrograms/dose nasal spray, solution

4.9 Overdose

Symptoms

The symptoms of active substance X overdose are expected to be an extension of its pharmacological actions e.g. lethargy, coma and severe respiratory depression. Other symptoms may be hypothermia, decreased muscle tonus, bradycardia, hypotonia. Signs of toxicity are deep sedation, ataxia, miosis, convulsions and respiratory depression which is the main symptom.

Treatment

For management of respiratory depression immediate countermeasures should be started including physical or verbal stimulation of the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The half-life of the antagonist may be short, therefore repeated administration or continuous infusion may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube and oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, hypovolemia should be considered and the condition should be managed with appropiate parenteral fluid therapy.

Example 4-symptoms & management

Describe acute symptoms and signs and potential sequelae and management of overdose in man

Active substance X 250 mg film-coated tablets

4.9 Overdose

Symptoms

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with active substance X overdoses.

Management of overdose

After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for active substance X. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60 % for active substance X and 74 % for the primary metabolite.

Example 5-special populations

Describe acute symptoms and signs and potential sequelae and management of overdose in man

Information specifically observed in special populations

Active substance X 500 mg tablets

4.9 Overdose

Active substance X overdose may lead to central nervous system impairment especially if active substance X plasma levels are above 20 mg/l. No proven antidotes have been established for active substance X overdose. The patient should be followed closely, taking into account that impairment is reversible, but given the long half-life and the lipophilic nature of active substance X, it may take weeks to return to normal. Other effects should be treated symptomatically. Because of its lipophilic nature, active substance X is not likely to be dialysable.

It is recommended to increase frequency of active substance X plasma level monitoring (e.g. every two weeks) in patients at risk of overdose (e.g. in case of renal or hepatic impairment, obese patients or patients with a recent weight loss).

Example 6-paediatric population

Describe acute symptoms and signs and potential sequelae and management of overdose

Paediatric population

Active substance X 50 mg hard capsules

4.9 Overdose
Experience with doses higher than the recommended therapeutic dose is limited. Isolated cases of active substance X overdose have been reported spontaneously and in the literature. In the event of overdose the patient should be observed and appropriate symptomatic treatment given. Generally the reported outcome in these cases was "improved" or "recovered". Events that have been reported at different dose ranges are as follows:

Adult overdose: 1200 to 1600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite. 1800 to 3200 mg (as high as 3200 mg daily for 6 days): Weakness, myalgia, increased creatine phosphokinase, increased bilirubin, gastrointestinal pain. 6400 mg (single dose): One case reported in the literature of one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, decreased neutrophil count, increased transaminases. 8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

Paediatric overdose:
One 3-year-old male exposed to a single dose of 400 mg experienced vomiting, diarrhoea and anorexia and another 3-year-old male exposed to a single dose of 980 mg dose experienced decreased white blood cell count and diarrhoea. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

Example 7-paediatric population

Describe acute symptoms and signs and potential sequelae and management of overdose

Paediatric population

Active substance X 200 mg powder for solution for infusion

4.9 Overdose
In clinical trials there were 3 cases of accidental overdose. All occurred in paediatric patients, who received up to five times the recommended intravenous dose of active substance X. A single adverse reaction of photophobia of 10 minutes duration was reported.
There is no known antidote to active substance X.
Active substance X is haemodialysed with a clearance of 121 ml/min. In an overdose, haemodialysis may assist in the removal of active substance X from the body.

Thank you for consulting this training presentation

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Please note the presentation includes examples that may have been modified to best illustrate the related principle