

Salicylate Poisoning

Pages with reference to book, From 160 To 161

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Abstract

Salicylate poisoning continues to be an important cause of drug related mortality. The zero order kinetics of salicylates at high doses is responsible in part for cases of iatrogenic poisoning. Serum levels tend to correlate with severity of poisoning in acute overdose cases only. Clinical manifestations include involvement of nervous system, hepatic and pulmonary systems alongwith metabolic disturbances. Measures at enhancing elimination and reducing absorption, while providing supportive care form the basis of management.

Introduction

Salicylate poisoning is said to be an easily diagnosed and treated entity with a low mortality. However, recent reviews have shown that an entity that was once predominantly a paediatric disease is no longer confined by chronological age and still carries a significant mortality^{1,2}. The intoxication could be from acute overdose or chronic use. In the acute setting the overdose is either an accidental ingestion in children or a suicidal attempt in the adults. In such cases, the history including previous drug overdosing, clinical presentation, presence of empty bottles and a reasonably good correlation between the drug level and the clinical severity generally leads to an easily diagnosed and treated condition. In chronic overdose cases, the poor correlation between plasma drug levels and clinical toxicity, different pharmacokinetics with the use of higher dosages and the delayed diagnoses accounts for the higher mortality seen with the chronic use of salicylates³⁻⁵.

Absorption and metabolism

Salicylates are readily absorbed from the gastrointestinal tract and circulate in the plasma in bound form. The absorption can continue for upto 24 hours or even longer. The delayed absorption is due to use of enteric coated preparation and also due to the formation of gastric acid-drug concretions and pylorospasm. Ninety percent of the drug is protein bound, mainly to albumin. At physiological pH about 99% of the free drug is ionized and not readily diffusible across the cell membrane. Since it is the tissue level of the drug that determines the end organ response, it logically follows that factors such as low albumin and acidosis result in increased toxicity⁶.

Metabolism of salicylates is dependent on the serum concentration of the drug⁷. At levels below 1.4 mmol/L (20 mg/dl), the elimination is proportional to the serum level i.e., first order kinetics. At higher levels, the metabolism becomes saturable i.e., changes to zero order kinetics. The saturable metabolism is due to the fact that the formation of salicylic acid (accounting for 75% of salicylate metabolism) cannot exceed beyond a fixed ceiling. Thus the dose increment for salicylates should be small.

Salicylate and its metabolites are excreted through the kidneys. The excretion is dependent on the glomerular filtration rate and urinary pH. Diuresis and alkalinization of urine can result in upto twenty fold increase in salicylate excretion⁸.

Clinical and laboratory manifestations

Salicylate poisoning is manifested clinically by disturbances of several organ systems, including central nervous, cardiovascular, pulmonary, hepatic, renal and metabolic systems⁹. Serum salicylate levels correlate only moderately with the clinical picture. In acute overdose, the level may be high without significant clinical signs while conversely in chronic ingestion levels in high therapeutic range may be

associated with significant clinical toxicity. The use of Done's nomogram is limited in its utility in cases of acute overdoses and when sufficient time has elapsed for complete absorption¹⁰. Levels are also subject to change over a short period of time secondary to delayed absorption and any changes in the acid-base status. Central nervous system effects are due to direct stimulation of the medullary respiratory center. The use of other drugs e.g., sedatives, can modify the respiratory stimulant effect. Direct irritation of the gastrointestinal tract and stimulation of the medullary chemoreceptor zone accounts for the nausea and vomiting. Dehydration results from gastrointestinal, skin and insensible fluid losses. Electrolyte disturbances include hypokalaemia and hypocalcaemia, which clinically are manifested by arrhythmias, tetany and seizures. Increased capillary permeability leads to adult respiratory distress syndrome¹¹. Hepatic dysfunction along with decreased platelet adhesiveness leads to bleeding problems. Uncoupling of the mitochondrial oxidative phosphorylation results in accumulation of organic acid which results in increased anion gap acidosis. The acid base disturbances form a continuum from respiratory alkalosis to compensated metabolic acidosis to frank metabolic acidosis. However, the most common acid base disturbance is a combined respiratory alkalosis and metabolic acidosis¹². Recently increased levels of phospholipase A2 have been reported in salicylate poisoning¹³.

Management

Principles of management include limiting the absorption, enhancing elimination, correction of metabolic abnormalities and supportive care. There is no specific antidote for salicylates. Due to delayed absorption and concrete formation the gastric emptying could be effective up to 24 hours following the acute ingestion. Activated charcoal in multiple oral doses is recommended to minimize absorption¹⁴. The possibility of the reversible adsorption of aspirin to charcoal resulting in delayed absorption is another reason for repeated charcoal doses¹⁵. Salicylate elimination is enhanced by alkaline diuresis, haemodialysis and haemoperfusion. The choice of method depends on the severity of poisoning. In general extracorporeal methods (haemoperfusion or haemodialysis) should be used in presence coma, seizures, cerebral and pulmonary oedema. In cases of acute ingestion when plasma levels exceed 6.5 mmol/L (90 mg/dl) or 5.4 mmol/L (75 mg/dl) in presence of renal failure, extracorporeal removal should be employed¹⁶. Alkaline diuresis should not be used in patients with blood pH greater than 7.5, oliguric renal failure, congestive cardiac failure, cerebral and pulmonary oedema. Arterial blood gases should be checked frequently to avoid and treat acidosis so as to minimize intracellular movement of salicylates. This is accomplished by proper adjustment of the ventilator settings and if necessary use of bicarbonate infusion. The use of glucose containing intravenous solution is important for protection of cerebral hypoglycaemia which can occur even in the presence of normal serum glucose levels¹⁷. Potassium supplementations are usually needed and calcium infusion may also be required. Positive pressure ventilation is required for the adult respiratory distress syndrome. Bleeding diathesis can be corrected by vitamin K, fresh frozen plasma and platelet transfusion.

Conclusions

Salicylate overdose should be suspected in patients taking salicylates chronically and manifesting unexplained acid base disturbances. At least a quarter of patients presenting with chronic salicylate poisoning are initially undiagnosed. These tend to be elderly, taking non-prescription drugs and with multiple underlying diseases. Higher level of clinical suspicion, appropriate incremental increase in doses and appropriate treatment should further reduce the incidence and improve outcome from salicylate poisoning.

References

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