## CASE REPORT

# Methomyl-Induced Severe Acute Pancreatitis: Possible Etiological Association

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### ABSTRACT

**Context** N-methyl carbamate insecticides are widely used in homes, gardens and agriculture. They share the capacity to inhibit cholinesterase enzymes with organophosphates and therefore share similar symptomatology during acute and chronic exposures. One of the serious effects of organophosphate and carbamate intoxication is the development of acute pancreatitis and subsequent intrapancreatic fluid formation.

Case report An 18-year old Caucasian man was admitted to our Intensive Care Unit with cholinergic crisis symptomatology, after the ingestion of an unknown amount of a carbamate insecticide (methomyl). Pseudocholinesterase levels were 2 kU/L on the day of admission (reference range: 5.4-13.2 kU/L). Two days after admission, an abdominal CT scan revealed blurring of the peripancreatic fat planes, inflammation and swelling of the pancreas, and a substantial amount of ascitic fluid in the left anterior pararenal space and pelvis. Paracentesis and analysis of the ascitic fluid demonstrated findings diagnostic of pancreatic ascites. There had been no other evident predisposing factors for acute pancreatitis, other than methomyl intoxication. Eleven days after admission, pseudocholinesterase levels returned to normal, while a new abdominal CT scan revealed the formation of intrapancreatic fluid collection. The patient was discharged in good physical condition two weeks after admission. A follow up abdominal CT scan performed one month later showed a significant reduction in the size of the intrapancreatic fluid.

Discussion is Acute pancreatitis not organophosphate uncommon after intoxication and carbamates share the same risk as organophosphorus pesticides. The development of acute pancreatitis and subsequent intrapancreatic fluid collection after methomyl intoxication has not previously been reported. This is the first case reported of acute pancreatitis and pancreatic anticholinesterase ascite formation after insecticide ingestion.

### INTRODUCTION

Carbamate insecticides are widely used in agriculture and home gardening [1, 2, 3]. They are derivatives of carbamic acid (as the organophosphates are derivatives of phosphoric acid) and, like organophosphates (OPs), their mechanism of action is that of inhibiting the vital enzyme cholinesterase (ChE) [1, 2, 3, 4]. ChE inhibition by carbamates is reversible but ChE inhibition by organophosphates is irreversible. This is why carbamate poisonings tend to be of shorter duration, unlike the permanent cholinesterase binding induced by organophosphates [4]. When ChE is inhibited by a carbamate, it is said to be "carbamylated", as an OP causes an enzyme to be "phosphorylated". In insects, the effects of OPs and carbamates are primarily those of poisoning of the central nervous system, since the insect neuromuscular junction is not cholinergic, as in mammals. The only cholinergic synapses known in insects are in the central nervous system.

N-methyl carbamate esters, by causing reversible carbamylation of the acetylcholinesterase enzyme, allow accumulation of acetylcholine (increase of acetylcholine activity) - the neuromediator substance - at parasympathetic neuroeffector junctions (muscarinic effects), at skeletal muscle myoneural junctions and autonomic ganglia (nicotinic effects), and in the brain (central nervous system effects) [1, 2, 3, 4]. At the cholinergic nerve junctions with smooth muscle and gland cells, high acetylcholine concentration causes muscle contraction and secretion, respectively. At the skeletal muscle junctions. excess acetylcholine may be excitatory (causing muscle twitching), but may also weaken or paralyze the cell by depolarizing the endplate. In the brain, elevated acetylcholine concentrations may cause sensory and behavioral disturbances, incoordination, and depressed motor function (rarely seizures), even though the N-methyl carbamates do not penetrate the central nervous system very efficiently. Respiratory depression combined with pulmonary edema is the usual cause of death from poisoning by N-methyl carbamate compounds. A serious side effect of organophosphate and carbamate intoxication is the development of acute pancreatitis1 [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12].

We describe the case of a patient who developed acute pancreatitis, pancreatic ascites and subsequent intrapancreatic fluid collection after the ingestion of methomyl, a carbamate insecticide. The development of acute pancreatitis and subsequent intrapancreatic fluid collection after methomyl intoxication has not previously been reported and this is the first case reported of acute pancreatitis and pancreatic ascite formation after anticholinesterase insecticide ingestion.

### CASE REPORT

An 18-year-old Caucasian man was admitted to our Intensive Care Unit with cholinergic crisis symptomatology, after the deliberate ingestion of an unknown amount of a carbamate insecticide (methomyl), in an unsuccessful suicide attempt. His family presented us with an empty bottle of a methomyl insecticide (Lannate), found in the kitchen. The patient was not on any medication, had no history of alcohol abuse and had an unremarkable medical record. On admission, the patient presented in comatose condition (Glasgow Coma Scale 3/15). His heart rate was 110 beats per minute and his blood pressure was 210/145 mmHg; he had labored breathing and tachypnea, excess sweating and his temperature was 37.5°C . Clinical examination revealed pinpoint pupils whereas auscultation of all the lung fields revealed rales as well as generalized rhonchi. He had profuse salivation and peristalsis of the gastrointestinal tract was markedly increased. There electrocardiographic were no abnormalities. Chest radiograph showed diffuse bilateral infiltrates. Heart size was normal. On blood gas analysis, the pH was 7.32 with HCO<sub>3</sub> 17 mmol/L, partial arterial

pressure of oxygen ( $Pa(O_2)$ ) was 56 mmHg and partial arterial pressure of carbon dioxide ( $Pa(CO_2)$ ) was 76 mmHg.

A complete blood count showed an elevation of the white blood cell count with neutrophil predominance. Glucose, ALP, creatine kinase and its isoform creatine kinase isoform MB were all increased while pseudocholinesterase levels were markedly decreased. The rest of the biochemical parameters measured on admission were within normal limits (Table 1). Urine microscopy was normal.

The patient was immediately transferred to the Intensive Care Unit where endotracheal intubation was performed since mechanical

Table 1. Laboratory values on admission an	d 2 days l	ater.
	Units	<b>Reference range</b>
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	Units	Reference range	On admission	After 2 days
Hematocrit	%	36-47	42	44
White blood cell count	$x10^{9} L^{-1}$	3.5-10.5	19.21	18.59
Neutrophil count	$x10^{9} L^{-1}$	2.3-8.7	17.2	16.4
Platelet count	$x10^{9} L^{-1}$	150-450	249	213
Blood glucose	mg/dL	60-100	237	88
Alkaline phosphatase (ALP)	IU/L	39-117	121	58
Aspartate aminotransferase (AST)	IU/L	3-40	29	39
Alanine aminotransferase (ALT)	IU/L	3-37	28	29
Gamma-glutamyltranspeptidase (GGT)	IU/L	9-35	-	25
Amylase	IU/L	25-100	-	325
Lactate dehydrogenase (LDH)	IU/L	250-450	423	797
Creatine kinase (CK)	IU/L	24-195	203	646
Creatine kinase isoform MB (CK-MB)	IU/L	0-25	27	32
Pseudocholinesterase	kU/L	5.4-13.20	2	4.3
Potassium	mmol/L	3.5-5.0	3.76	3.78
Sodium	mmol/L	135-143	143	142
Total protein	g/dL	6-8	7.81	5.43
Albumin	g/dL	3.5-5.20	5.15	3.24
Serum creatinine	mg/dL	0.5-1.3	1.68	1.37
Ascitic fluid amylase	IU/L	-	-	1,401
Ascitic fluid albumin	g/dL	-	-	2.88

ventilation was considered necessary. An orogastric tube was inserted and continuous gastric lavage as well as suction of bronchial secretions were continuously carried out, while all his clothes were taken off and the patient's skin was decontaminated using large amounts of water and soap. Two mg of atropine were given every 15 minutes intravenously order achieve in to atropinization (clearing of bronchial secretions, dry mouth). Pupil size was not considered end-point an of atropine administration.

A total of 60 mg of atropine was needed over the next 6 days in order to achieve the above goal.

The patient's level of consciousness was gradually ameliorated and artificial respiration was ended 32 hours later.

Two days after admission, he complained of upper abdominal steady pain with a band-like radiation to the back. Clinical examination revealed generalized abdominal tenderness and mild distension, without signs of peritoneal irritation. Bowel sounds were markedly decreased. Serum amylase levels were 325 IU/L (Table 1). Considering the abdominal distress of the patient and the high levels of serum amylase, pancreatitis was suspected and a computed tomography scan one hour later demonstrated blurring of peripancreatic fat planes, inflammation and swelling of the pancreas, and a substantial amount of ascitic fluid in the left anterior pararenal space and pelvis (Figure 1).

The imaging findings, along with serum amylase elevation and the patient's symptoms confirmed the diagnosis of acute pancreatitis. There had been no other predisposing factors



**Figure 1.** Dual phase CT showing blurring of peripancreatic fat planes, inflammation and swelling of the pancreas and a substantial amount of ascitic fluid in the left anterior pararenal space.

for acute pancreatitis were evident, other than methomyl intoxication. The Ranson criteria number on presentation was 2.

Paracentesis and analysis of the ascitic fluid performed the same day demonstrated findings diagnostic of pancreatic ascites: the combination of a serum-ascites albumin gradient below 1.1 g/dL and elevated ascitic fluid amylase (Table 1).

The patient was treated with total parenteral nutrition and imipenem.

The serial blood count over the next few days showed a decrease in all cell lines consistent with a dramatic improvement in the patient's symptoms. Serial biochemical values over the same period showed normalization of all parameters except amylase levels which were slightly above normal. Ranson's criteria during the first 48 hours remained two.

Pseudocholinesterase levels increased gradually, but remained below normal for 11 days.

Ten days after admission, a new abdominal CT scan revealed the formation of intrapancreatic fluid collection.

The patient was discharged in good physical condition 2 weeks after admission. A followup abdominal CT scan performed a month later showed a significant reduction in the size of the fluid collection.

## DISCUSSION

Acute pancreatitis as a complication of OP intoxication is not an uncommon condition. Its incidence in adults is 12.76% [6] and is higher in children [3]. Carbamates share the same risk of pancreatitis as OP pesticides [4]. Usually, complications - such as pancreatic necrosis - are quite rare [7, 11] and they can also occur secondary to cutaneous exposure to an organophosphate [8]. However, mortality following OP poisoning remains high despite adequate respiratory support, intensive care, and specific therapy with atropine. One-third of the patients needing mechanical ventilation and reaching Intensive Care Units die within the first 72 h of poisoning. Systolic blood pressure of less than 100 mmHg and the necessity of a FiO<sub>2</sub> greater than 40% to

maintain adequate oxygenation are predictors of a poor outcome in patients mechanically ventilated in the Intensive Care Unit [13].

In previous case reports, severe acute pancreatitis with pseudocyst formation has been described in an adult woman following accidental ingestion of an anticholinesterase insecticide [11] and in an adult man after the ingestion of a carbamate insecticide after an unsuccessful suicide attempt [12]. This case describes the formation report of intrapancreatic fluid collection after the ingestion of an anticholinesterase insecticide. Significant fluid collections develop in 30-60% of cases of acute pancreatitis [14].

Regarding carbamate intoxication, four cases of acute pancreatitis have been reported [4, 5, 9, 12], but this is the first one following methomyl ingestion.

Pancreatic ductal hypertension and stimulation of exocrine pancreatic secretion secondary to cholinergic stimulation are considered to be responsible for the development of pancreatitis [1, 2, 3, 4, 15]. Furthermore, organophosphates such as echothiophate. which inhibit the two cholinesterase isoenzvmes (butyrylcholinesterase and acetylcholinesterase) in the human pancreas, sensitivity increase pancreatic to acetylcholine [1, 2].

We treated the patient with total parenteral nutrition and imipenem according to recent studies which demonstrated improved associated with outcome the use of prophylactic antibiotics in patients with severe necrotizing pancreatitis [16, 17, 18, 19]. In addition, a meta-analysis of 8 controlled trials concluded that prophylactic broad-spectrum antibiotic administration reduced mortality in patients with severe [20]. acute pancreatitis However. а subsequent multicenter, placebo-controlled trial of prophylactic antibiotics in severe acute pancreatitis, which was not included in the above meta-analysis, found that there was no benefit. [21].

We recognize the possibility that there was the pancreatic inflammation as a result of the hypoxemic effect on the pancreas [4, 12]. This is the first case reported of acute pancreatitis and pancreatic ascite formation after anticholinesterase insecticide ingestion.

#### CONCLUSION

A serious adverse effect of carbamate intoxication is the development of acute pancreatitis which, depending on the severity of the inflammation, can lead to the development of complications such as pancreatic ascites, intrapancreatic fluid and/or pancreatic pseudocyst formation.

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**Abbreviations** ALP: alkaline phosphatase; OPs: organophosphates; ChE: cholinesterase

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#### References

1. Kandalaft K, Liu S, Manivel C, Borner JW, Dressel TD, Sutherland DE, Goodale RL. Organophosphate increases the sensitivity of human exocrine pancreas to acetulcholine. Pancreas 1991; 6:398-403. [PMID 1715083]

2. Goodale RL, Manivel JC, Borner JW, Liu S, Judge J, Li C, Tanaka T. Organophosphate sensitizes the human pancreas to acinar cell injury: an ultrastructural study. Pancreas 1993; 8:171-5. [PMID 8460092]

3. Weizman Z, Sofer S. Acute pancreatitis in children with anticholinesterase insecticide intoxication. Pediatrics 1992; 90:204-6. [PMID 1379357]

4. Moritz F, Droy JM, Dutheil G, Melki J, Bonmarchand G, Leroy J. Acute pancreatitis after carbamate insecticide intoxication. Intensive Care Med 1994; 20:49-50. [PMID 8163760]

5. Lee HS. Acute pancreatitis and organophosphate poisoning. A case report and a review. Singapore Med J 1989; 30:599-601. [PMID 2635407]

6. Sahin I, Onbasi K, Sahin H, Karakaya C, Ustun Y, Noyan T. The prevalence of pancreatitis in organophosphate poisonings. Hum Exp Toxicol 2002; 21:175-7. [PMID 12099618]

7. Panieri E, Krige JE, Bornman PC, Linton DM. Severe necrotizing pancreatitis caused by organophosphate poisoning. J Clin Gastrenterol 1997; 25:463-5. [PMID 9412952]

8. Marsh WH, Vukov GA, Conradi EC. Acute pancreatitis after cutaneous exposure to an organophosphate insecticide. Am J Gastroenterol 1988; 83:1158-60. [PMID 3421227]

9. Singh S, Parthasarathy S, Sud A, Wanchu A, Bambery P. Acute pancreatitis following propoxyfur (Baygon) ingestion. J Assoc Physicians India 2003; 51:78-9. [PMID 12693465]

10. Lankisch PG, Muller CH, Niederstadt H, Brand A. Painless acute pancreatitis subsequent to anticholinesterase insecticide (Parathion) intoxication. Am J Gastroenterol 1990; 85:872-5. [PMID 2371989]

11. Dressel TD, Goodale RL, Arneson MA, Borner JW. Pancreatitis as a complication of anticholinesterase insecticide intoxication. Ann Surg 1979; 189:199-204. [PMID 426552]

12. Rizos E, Liberopoulos E, Kosta P, Efremidis S, Elisaf M. Carbofuran-Induced Acute Pancreatitis. JOP. J Pancreas (Online) 2004; 5:44-7. [PMID 14730122]

13. Munidasa UA, Gawarammana IB, Kularatne SA, Kumarasiri PV, Goonasekera CD. Survival pattern in patients with acute organophosphate poisoning receiving intensive care. J Toxicol Clin Toxicol 2004; 42:343-7. [PMID 15461241]

14. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg 1993; 128:586-90. [PMID 8489394]

15. Dressel TD, Goodale RL Jr, Zweber B, Borner JW. The effect of atropine and duct decompression on the evolution of Diazinon-induced acute canine pancreatitis. Ann Surg 1982; 195:424-34. [PMID 6175284]

16. Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, et al. Early antibiotic treatment in acute necrotizing pancreatitis. Lancet 1995; 346:663-7. [PMID 7658819]

17. Pederzoli P; Bassi C; Vesentini S; Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 1993; 176:480-3. [PMID 8480272]

18. Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. Pancreas 1996; 13:198-201. [PMID 8829189]

19. Bassi C, Falconi M, Talamini G, Uomo G, Papaccio G, Dervenis C, et al. Controlled clinical trial

of pefloxacin versus imipenem in severe acute pancreatitis. Gastroenterology 1998; 115:1513-7. [PMID 9834279]

20. Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis: A meta-analysis. J Gastrointest Surg 1998; 2:496-503. [PMID 10457308]

21. Isenmann R, Runzi M, Kron M, Kahl S, Kraus D, Jung N, et al. Prophylactic antibiotic treatment in patients with predicted acute pancreatitis: a placebocontrolled, double-blind trial. Gastroenterology 2004; 126:997-1004. [PMID 15057739]