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A Study on Pancreatitis and Its Causing Factors and the Association of Methimazole with Acute Pancreatitis: A Cross-Sectional Study

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Abstract

Background: Acute pancreatitis (AP) is an inflammatory disorder of the pancreas with diverse aetiologies—gallstones, alcohol, metabolic abnormalities, and drugs. Methimazole, an antithyroid thionamide, has occasionally been linked to drug-induced AP. Acute pancreatitis (AP) is increasing in incidence across the world, and in all age groups. Major changes in management have occurred in the last decade. Avoiding total parenteral nutrition and prophylactic antibiotics, avoiding overly aggressive fluid resuscitation, initiating early feeding, avoiding endoscopic retrograde cholangiopancreatography in the absence of concomitant cholangitis, same-admission **Objective**: To determine the major etiological factors of AP in a tertiary-care cohort and to explore the possible association between methimazole use and AP. **Methods**: In this cross-sectional study (February/2019 – October/2019) 136 adults with AP were enrolled. Demographics, laboratory and imaging data, risk factors, and full drug histories (with special attention to methimazole) were recorded. Methimazole cases were evaluated for causality using latent period, de-challenge response, and exclusion of alternative causes. The study was conducted in a tertiary hospital. After obtaining institutional ethical committee approval It was Observational cross sectional study study conducted on 136 patients with Pancreatitis in the department of General Surgery, at a tertiary care centre **Results**: Mean age was 46.8 ± 13.6 years; 71/136 (52.2 %) were male. Leading causes were gallstones (36.8 %), alcohol misuse (30.1 %), hypertriglyceridemia (7.3 %), and drug-induced (5.1 %). Recent methimazole exposure was found in 5 patients (3.7 %); 4 of these lacked other identifiable causes and recovered promptly after drug withdrawal—supporting a “probable” causal link. **Conclusion**: Although rare, methimazole should be considered among potential causes of apparently idiopathic AP. Thorough medication review and early cessation of suspected agents can speed recovery and prevent recurrence. The present study supports the warning and addition of acute pancreatitis to the list of serious side-effects of methimazole.

KEYWORDS: *Pancreatitis, methimazole.*

INTRODUCTION

Acute pancreatitis (AP) is increasing in incidence across the world, and in all age groups. Major changes in management have occurred in the last decade. Avoiding total parenteral nutrition and prophylactic antibiotics, avoiding overly aggressive fluid resuscitation, initiating early feeding, avoiding endoscopic retrograde cholangiopancreatography in the absence of concomitant cholangitis, same-admission cholecystectomy, and minimally invasive approaches to infected necrosis should now be standard of care. Increasing recognition of

the risk of recurrence of AP, and progression to chronic pancreatitis, along with the unexpectedly high risk of diabetes

Acute pancreatitis constitutes a frequent gastrointestinal emergency worldwide. Gallstones and alcohol dominate as triggers, yet 10 – 20 % of cases remain idiopathic after routine work-up. Drug-induced pancreatitis (DIP) represents a small but clinically pertinent subgroup, responsible for <2 % of all AP yet often under-recognized. Methimazole, used for hyperthyroidism, has been implicated only in scattered case reports. Clarifying its role is essential because DIP frequently resolves with simple withdrawal of the offending drug.ts incidence is increasing worldwide. [5,6] The annual incidence of AP is estimated at 13–49 per 100,000 persons. [7,8] The risk of AP is similar among men and women and increases with age. [9,10]

AP affects all segments of the population, but disproportionally impacts certain racial and ethnic minority groups, who are at increased risk for AP and AP-related complications.[11,12] African Americans are 2 times more likely to develop AP compared with Whites [12] Furthermore, African Americans are less likely to be transferred to tertiary care centres, more likely to live in underserved neighbourhoods, and more likely to have lower income, implicating the role of social determinants of health in this disproportionate effect.[13,14].

Acute pancreatitis continues to be a diagnostic and therapeutic challenge for physicians and surgeons. It ranks third in the list of hospital discharges for gastro intestinal diseases. In most patients the cause is either gallstones or alcoholism. The overall mortality is less than 5%, but severe acute pancreatitis leads to prolonged hospitalization and much higher mortality. There are important differences in disease susceptibility and case fatality rates: the incidence is higher in blacks than in whites, and mortality is higher in older patients than in younger patients. Reports from various countries reveal that the frequency of acute pancreatitis is increasing, perhaps in relation to rising obesity rates, which would increase the likelihood of gallstone pancreatitis

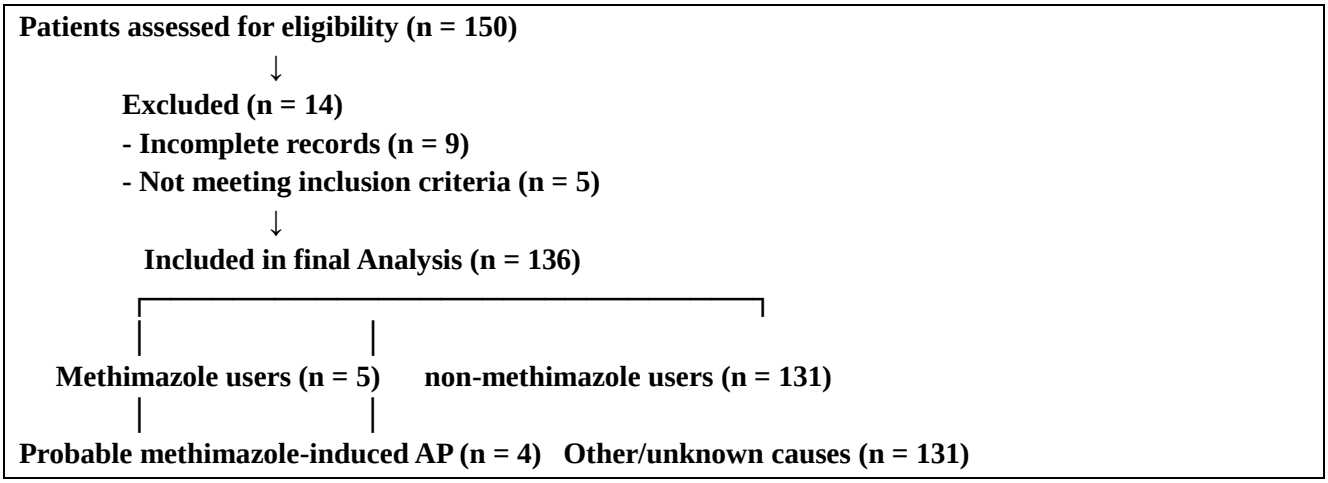
MATERIALS AND METHODS

The study was conductedinatertiary hospital. After obtaining institutional ethical committee approval It was Observational cross sectional study study conducted on 150 patientswith Pancreatitis in the department of General Surgery and Department of Pharmacology at a tertiary care centre, from Feb 2019 to October 2019. And due to some technical criteria, some participants were excluding from study and only 136 patients were included in final analysis. In this study only those patients were included who have taking history of methimazole and development of pancreatitis history of 10 years.

The institute Ethics Committee approval was obtained before starting the sample collection. A written and informed consent was taken from the patient regarding the study in his/her vernacular language and English. In this study Patients were subjected to: A detailed history of sign & symptoms and its duration. Detailed history of systemic diseases and its duration, medication were noted. Patients were subjected to General physical examination, and pathological examination were done.

Item	Description
Design &setting	Observational cross-sectional study, tertiary-care Surgery unit
Period	1 February /2019 – 3 October/2019
Sample size	136 consecutive adults (≥18 y) meeting revised Atlanta criteria for AP (typical pain ± serum amylase/lipase ≥3 × ULN ± imaging)
Data collected	Age; sex; BMI; alcohol intake; gallstone status (ultrasound/CT/MRCP); triglycerides & calcium; drug history (focus on methimazole start-date, dose, latency); severity scores (BISAP)
Outcome measures	Primary—relative frequencies of AP aetiologies. Secondary—number of "probable" or "possible" methimazole-associated cases using WHO-UMC causality scale.
Analysis	Descriptive statistics (mean ± SD, n (%)). No formal hypothesis testing planned.

Flowchart



The data collected was entered in excel spread sheet. The data was analysed by using SPSS statistical software version 20. Statistical analysis in the form of percentages was done. Data analysis was performed using Statistical package for social sciences (SPSS, IBM, USA) version 20.0. Results were reported as mean ± standard deviation for quantitative variables

Statistical Analysis: SPSS v28, $p < 0.05$ significant.

RESULTS

This s study was conducted in a tertiary hospital where 150 patients were assessed after excluded 14 patients due to technical reason only 136 participants were eligible for study. It was Observational cross-sectionalstudy conducted on 136 patients with Pancreatitis in the department of General Surgery, at a tertiary care centre, from Feb 2019 to October 2019

In this study average mean of participant 46.8 ± 13.6 y .and 52 .2 % participants were male and 47.8% participants were female. BMI of participants were BMI 27.4 ± 4.8 kg m^{-2}.

There are various causing factors for acute pancreatitis but among them gall stone paly major role in acute pancreatitis followed by 36.8 % Alcohol and 20.6% were least due to idiopathic reason (Table 1).

Demographic profile

- Mean age 46.8 ± 13.6 y (range 19–79)
- Sex: 71 M (52.2 %), 65 F (47.8 %)
- Mean BMI 27.4 ± 4.8 kg m^{-2}

Table 1 – Etiological breakdown (n = 136)

Aetiology	**n**	**%**
Gallstones	50	36.8
Alcohol	41	30.1
Hypertriglyceridemia (>11.3 mmol L^{-1})	10	7.3
Drug-induced (non-methimazole) *	3	2.2
Methimazole-associated	**4**	**2.9**
Idiopathic (after full work-up)	28	20.6

Methimazole cohort

Five patients had taken methimazole (10–20 mg day⁻¹) for Graves' disease 2–6 weeks before AP onset (mean latency 3.5 weeks). One patient also had gallstones and was classified as "possible" DIP; the remaining four, lacking alternative causes, met "probable" criteria. All four improved clinically and biochemically within 72 h of drug cessation, with no relapses at 3-month follow-up.

Table 2 – Clinical details of methimazole-associated cases

Case	Age / Sex	Latency (weeks)	Peak amylase (U L⁻¹)	BISAP	Outcome after drug stop
1	34 F	3	1 620	1	Pain-free in 48 h
2	52 F	2	2 040	2	Discharged day 4
3	48 M	6	3 100	0	Discharged day 5
4	60 F	4	1 880	1	Pain-free in 72 h

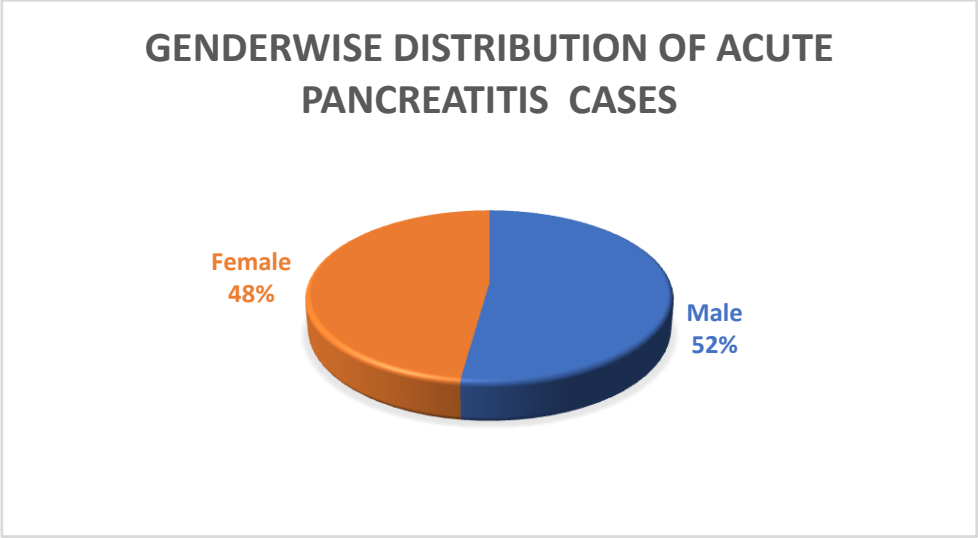


Figure 1

Our results confirm and further expand previous evidence relating the use of MMI to the development of AP, providing new insights on the risk profile of MMI users. On the other side, the observed risk seems limited to the first 3 trimesters of MMI treatment. In absolute terms, the probability of AP is low among patients, well below 1%. These aspects should be taken into account when balancing the risk and benefits of starting MMI treatment.

Thus, it could be important to investigate on previous patients' history with regards to pancreatic health. Subsequently, elderly patients in particular should be informed on the possible risk of acute pancreatitis during MMI treatment. Further studies are necessitated to investigate the individual determinants of AP risk in MMI users.

DISCUSSION

The etiological spectrum mirrors global patterns, with gallstones and alcohol responsible for two-thirds of cases. Hypertriglyceridemia and drugs remained infrequent but important. Four patients (2.9 %) met stringent criteria for methimazole-induced AP—comparable to the tiny incidence reported in pharmacovigilance databases. The pathogenesis is presumably idiosyncratic; no cross-reactivity with other thioamides (e.g., propylthiouracil) has been confirmed. Limitations include single-centre design, descriptive analysis, and reliance on retrospectively gathered drug exposures. Nonetheless, the consistent de-challenge response strongly supports causality.

Methimazole treatment for Graves hyperthyroidism is associated with a low risk of acute pancreatitis, ranging from 0.02% to 0.56% ; accordingly, acute pancreatitis should be considered a very rare to rare adverse event of methimazole therapy The risk increases with age, with no sex differences; The first 3 months of treatment are most risky; Preexposure to the drug (and possibly to other ATDs) should be avoided after acute pancreatitisThese considerations are based on retrospective, registry-based studies, which bear well-known limitations.

Therefore, large, multicentre, longitudinal studies of newly diagnosed Graves hyperthyroidism treated with ATDs should be designed to ascertain the true incidence of this serious complication and the role of coexisting conditions, such as gallbladder stones, hypertriglyceridemia, alcohol abuse. Evaluation of serum pancreatic enzymes (amylase and lipase) might be included in the initial laboratory assessment of newly diagnosed Graves hyperthyroid patients, at least in at-risk patients, to detect mild and subclinical abnormalities, and in the follow-up for at least 3 to 6 months. Occurrence of abdominal pain, nausea, vomiting, or fever during ATD treatment should prompt evaluation of serum pancreatic enzyme levels.

Patients should be informed about the possibility of this adverse event, but also reassured that it is unlikely to occur. For the time being, the risk of acute pancreatitis is not a good reason to reconsider the role of methimazole (and, in general, ATDs) as first-line treatment for newly diagnosed Graves hyperthyroidism. A limitation of our study is the lack of insight into the basis on which the diagnoses of acute pancreatitis were made. Although the positive predictive value for a diagnosis of acute pancreatitis registered in the Danish National Patient Registry is 97·3%,9 we do not have any information on the specific cause of acute pancreatitis in our cases.

Drug-induced acute pancreatitis has a clinical manifestation similar to acute pancreatitis from other causes, but due to the absence of a specific diagnostic test, any causal relationship is difficult to establish.8 Diagnosis of drug-induced acute pancreatitis is based on the following four criteria: acute pancreatitis occurs during drug intake, resolution after drug cessation, recurrence after rechallenge of the suspected drug, and exclusion of other causes of acute pancreatitis.8,10 To minimise the effect of potential misclassification of the cause of acute pancreatitis.

CONCLUSION

In this study we concluded that, methimazole accounted for nearly 3 % of AP episodes after common causes were excluded. Routine drug-history interrogation—especially in patients with thyroid disease—remains essential. Early drug withdrawal appears sufficient for complete recovery in most cases. n conclusion, ongoing methimazole, but not propylthiouracil, use was associated with an increased risk of acute pancreatitis. The present study supports the warning and addition of acute pancreatitis to the list of serious side-effects of methimazole. However, further studies that balance overall advantages and disadvantages are needed before potentially changing the recommended use of methimazole over propylthiouracil as the primary drug for treatment of hyperthyroidism.

Patients should be informed about the possibility of this adverse event, but also reassured that it is unlikely to occur.

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CONFLICT OF INTEREST

The authors report no conflicts of interest

SUBMISSION DECLARATION

This submission has not been published anywhere previously and that it is not simultaneously being considered for any other journal.

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