MAO inhibitors and coronary artery surgery: a patient death

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The mechanisms of action of monoamine oxidase inhibitors (MAOIs) suggest that patients taking them may respond with hyper- or hypotension when undergoing coronary artery surgery. We describe a case where MAOIs were present and fentanyl and midazolam were the anaesthetic agents used. The anaesthesia and surgery were performed without incident. Postoperative ICU care was complicated by hypertension, hyperthermia, and severe shivering followed by hypotension resistant to therapy and finally death. Diagnoses of pulmonary embolism and sepsis were unproven and may have played a role. The MAOIs may also have played a role. Reactions in patients while taking both meperidine and MAOIs are unusual and animals react differently from humans to a combination of MAOIs and narcotics. There are only five reported cases where fentanyl was given to patients on MAOIs. We conclude that, until there is more information, MAOIs should be discontinued, if possible, before surgery in which catecholamines may be needed.

Notre connaissance du mécanisme d'action des inhibiteurs de la monoamine oxydase (IMAO) porte à croire que cette médication peut provoquer une réaction hypo- ou hypertensive pendant la chirurgie des artères coronaires. Nous décrivons une observation au cours de laquelle chez un patient déjà sous IMAO, on a utilisé du fentanyl et du midazolam comme anesthésiques. Les soins postopératoires en unité de soins intensifs se sont compliqués d'hypertension, d'hyperthermie et d'un frisson violent suivis d'une hypotension rebelle à tout traitement et finalement du décès. Des diagnostics d'embolie pulmonaire et de septicémie, bien que mis en cause, n'ont pu être confirmés. L'IMAO

Key words

ATARACTIC AGENTS: MAO inhibitors;
COMPLICATIONS: death;
SURGERY: cardiac.

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aurait aussi pu contribuer à cette issue fatale. Alors que les réactions chez des patients qui prennent de la mépéridine et de l'IMAO sont rares, les animaux réagissent différemment des humains à l'association IMAO-opiacés. Seulement cinq observations de patients sous IMAO et recevant du fentanyl sont rapportées. Nous concluons qu'il est préférable de cesser les IMAO chez les patients pour lesquels on pourrait avoir recours à des.

Current recommendations^{1,2} concerning the anaesthetic management of patients receiving monoamine oxidase inhibitors (MAOI) suggest that there is no need to discontinue MAOIs before surgery; morphine or fentanyl may be used; meperidine should be avoided; and the classic triad of "hypoxia, hypercarbia and hypotension" be avoided.

We attempted to follow these guidelines and present a case where MAOIs were continued up to the time of coronary artery bypass grafting (CABG). We are not certain of the underlying cause of death in the ICU but suggest that MAOIs may have played a role and complicated patient management.

Case report

A 64-yr-old man with unstable angina presented for CABG. He was depressed and receiving tranlycypromine (MAOI) 30 mg bid for ten years, chlorthalidopexide 25 mg bid and flurazepam. He had myelodysplasia (Hb 87 g · dl⁻¹, WBC 4.9 · 10⁶ · L⁻¹). He had had a myocardial infarction two months before surgery with continuing angina while taking digoxin, furosemide, aspirin, nitroglycerine paste, metoprolol and diltiazem. He was a smoker and while in hospital developed a left lower lobe (LLL) pneumonia requiring tracheal intubation and pulmonary ventilation for four days. Investigation revealed a normal cardiac output (Q), pulmonary wedge pressure (Pw) and matched LLL abnormalities on V/Qscan. He was treated with cefoxitin, salbutamol and ipratropium and one month before surgery the chest cleared on physical examination and chest radiography. He was also receiving omeprazole, iron, domperidone, and sulcralfate. On physical examination he was a large man (surface area 2 m²) and appeared pale but in no distress. Blood pressure was 169/80 mmHg supine and 90/50 mmHg standing.

Jugular venous pressure was low and there was no peripheral oedema. The respiratory rate was 12 per min. There were no adventitious sounds.

Persantine thallium scanning demonstrated severe septal, inferior and apical ischaemia and a myocardial infarction in the inferior wall. At coronary catheterization the left main coronary artery was 80% obstructed and the right coronary artery was dominant. Therefore he was placed on an urgent list for CABG. The aspirin was stopped but all other medication was continued including tranlycypromine.

A CABG surgery was performed without difficulty. The preoperative laboratory and cardiovascular data are shown in Table I. Premedication consisted of morphine 12.5 mg, perphenazine 2.5 mg, isosorbide 15 mg, metoprolol 100 mg, and diltiazem 60 mg. The anaesthetic was fentanyl 7 mg, midazolam 7 mg, and pancuronium 20 mg. Two coronary vessels were grafted successfully. The operative course of the patient was stable at all times including weaning from cardiopulmonary bypass. No inotropes were required in the operating room at any time.

Postoperatively the patient was initially stable but management became increasingly difficult. First, there was uncommonly severe shivering and resistant hypertension. Then, labile hypotension, a high cardiac output and a fever developed.

GLOSSARY OF TERMS

BP	– Blood pressure (mmHg)
HR	– Heart rate (min^{-1})
Q	– Cardiac output ($\text{L} \cdot \text{min}^{-1}$)
CI	– Cardiac index ($\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)
PPa	– Pulmonary artery pressure (mmHg)
PPad	– Pulmonary artery diastolic pressure (mmHg)
Pw	– Pulmonary wedge pressure (mmHg)
CVP	– Central venous pressure
IVC	– Inferior vena cava
CVS	– Cardiovascular system
CABG	– Coronary artery bypass grafting
VE	– Minute volume ($\text{L} \cdot \text{min}^{-1}$)
PEEP	– Positive end expiratory pressure ($\text{cm H}_2\text{O}$)
PE	– Pulmonary embolus
MAOI	– Monoamine oxidase inhibitors
NE	– Norepinephrine
E	– Epinephrine
Chlorpr	– Chlorpromazine
NTG	– Nitroglycerine
NTP	– Nitroprusside
DPM	– Dopamine
DBM	– Dobutamine
IABP	– Intra-aortic balloon pump
5 H-T	– 5 Hydroxy tryptamine

Immediate postoperative data (Table I, 13:00) indicated no problems. Fentanyl was given for sedation. The initial temperature was 35.7° C rectal and over hours gradually increased to 36.9° C associated with severe shivering. Over the same period hypertension developed. The increase in BP did not respond to nitroglycerine (NTG – 80 mg over two hours), nitroprusside (NTP – 25 mg over one hr), nifedipine (20 mg SL) or sedation (midazolam 15 mg and fentanyl 1 mg). By 20:00 (Table I) BP was 180 mmHg systolic. Finally chlorpromazine (12.5 mg *iv*) was tried. Meperidine was not used. Respiratory indices were normal.

The shivering continued despite normothermia. Hypotensive episodes developed (Table I, 21:15). The pulmonary artery diastolic to wedge pressure gradient widened and cardiac output increased. Neuromuscular blockade (vecuronium) was employed which controlled the shivering and NE was infused to increase BP. Blood gas analysis at 21:15 indicated a combined metabolic and respiratory acidosis, and hypoxaemia. Despite efforts to control these problems the patient had an asystolic cardiac arrest at 23:15 requiring four minutes of CPR. With epinephrine 1 mg *iv* normal sinus rhythm and BP returned.

The patient's temperature increased to 38° C over the next six hours (Table II, 6:00). Blood pressure could only be maintained with norepinephrine at 1.6 $\text{mg} \cdot \text{hr}^{-1}$. Cardiac output remained high, and PPad–Pw elevated (Table II, 6:00). Minute volume (VE) was increased (24:00) but PaCO_2 increased. Progressive increases in VE were required to control the respiratory acidosis (Tables I and II, 24:00 to 6:00). The chest radiograph indicated pulmonary oedema with the right lower lobe (RLL) spared. The WBC increased as did the serum creatinine concentration. The patient was heparinized, cultures were taken and gentamycin and cefazolin were administered. As the day progressed core temperature increased to 39° C despite cooling and continuous neuromuscular blockade. Cardiac output decreased and BP was difficult to maintain. Besides episodes of tachycardia the ECG remained unchanged. Dopamine and epinephrine were not successful in maintaining Q and so an IABP was inserted (Table II, 22:00). The A-a O_2 gradient widened, metabolic acidosis developed and urine output decreased. The patient became asystolic at 7:18 the next morning. Post mortem examination was not allowed. Two blood cultures and a urine culture were negative.

Discussion

The diagnosis of pulmonary embolus was considered in view of the high PPad–Pw gradient, the high dead space (PaCO_2 36 mmHg, VE 16 $\text{L} \cdot \text{min}^{-1}$ with muscle relaxation to reduce the CO_2 production of shivering) and the absence

TABLE I Patient cardiorespiratory data – Day 1

Time hr	Preop 9:00	Postop 13:00	Day 1 20:00	Day 1 21:15	Day 1 23:10	Day 1 24:00
BP mmHg	120/70	120/50	180/60	80/40	120/45	100/45
HR · min ⁻¹	60	60	80	115	88	94
Q L · min ⁻¹	6	6.2	9.6	11.2	11.6	8.8
CI L · m ⁻¹ · m ⁻²	3	3.1	4.8	5.6	5.8	4.4
PPa mmHg	46/18	42/16	42/16	49/31	62/30	73/33
Pw mmHg	15	14	14	21	15	20
Temp °C R	36.7	35.7	36.9	37.2	37.2	37.0
pH	7.48	7.39	7.38	7.29		7.08
PaCO ₂ mmHg	39	38	36	46		71
V E L · min ⁻¹		6	6	6		8
PaO ₂ mmHg	431	360	103	72		166
FiO ₂	1.0	0.9	0.4	0.4		1
PEEP cmH ₂ O	0	5	5	5		5
PVO ₂ mmHg						39
Hb g · dl ⁻¹	91	81	98			
WBC 10 ⁶ · L ⁻¹	4.5	11	6.9			
BUN mmol · L ⁻¹	7.7	6.2				
Cr mmol · L ⁻¹	159	117				
CVS			NTG		E	NE
Drugs			NTP Adalat Chlorpr		NE	

TABLE II Patient cardiorespiratory data – Days 2 and 3

Time Hr	Day 2 1:00	Day 2 6:00	Day 2 10:00	Day 2 14:00	Day 2 22:00	Day 3 2:00
BP mmHg	100/50	110/60	115/60	95/65	95/45	85/60
HR · min ⁻¹	90	90	125	130	145	145
Q L · min ⁻¹	9.4	5.2	4.2	3.1	7.7	2.4
CI L · m ⁻¹ · m ⁻²	4.7	2.6	2.1	1.6	3.9	1.2
PPa mmHg	49/29	46/31	44/31	40/31	48/30	50/38
Pw mmHg	20	17	19	24	22	23
Temp °C R	36.9	38.3	37.9	38.5	37.3	37.6
pH	7.28	7.31	7.38	7.26	7.25	7.30
PaCO ₂ mmHg	40	36	32	30	43	33
VE L · min ⁻¹	11.2	16	20	20	20	20
PaO ₂ mmHg	186	94	66	121	56	113
FiO ₂	0.8	0.8	0.8	0.8	1.0	1.0
PEEP cmH ₂ O	5	7.5	10	12.5	10	15
PVO ₂ mmHg			35		34	
Hb g · dl ⁻¹			123	134	99	
WBC 10 ⁶ · L ⁻¹			22.8	19.3	20.1	
BUN mmol · L ⁻¹			8.7	9.9		
Cr mmol · L ⁻¹			167	217		
CVS	NE	NE	NE	NE	NE	NE
Drugs	DPM		DPM	E	DPM E IABP	DBM E IABP

of perfusion of the RLL on the chest radiograph. A pulmonary angiogram was not carried out because the patient was unstable, kidney failure was imminent and the dye dangerous; we would not have removed a pulmonary embolus (PE) even if it were diagnosed since the cardiac output was high and we would not have inserted an inferior vena cava umbrella at the first embolus. However, the high cardiac output indicated a diagnosis other than pulmonary embolus. An error in the measurement of $\dot{Q}$ was considered. The temperature measured by the thermistor on the PA catheter agreed with another independent temperature measurement. Two cardiac output machines gave the same answer. An intracardiac shunt could have resulted in a falsely high $\dot{Q}$. But there was no change in PO_2 from the CVP to right ventricle to PA ports (therefore not a left to right shunt) and high levels of PEEP improved PaO_2 (suggestive it was not a right to left cardiac shunt). Therefore $\dot{Q}$ appeared to be correct.

Sepsis was considered given the high cardiac output, shivering, fever and a high WBC in a patient with myelofibrosis. However, no source was found and cultures of blood and urine were negative. There was no response to antibiotic therapy.

A transfusion reaction may have occurred. Although the patient initially received only his own blood back from the pump, he was transfused with six units of platelets. Therefore the shivering and fever may have represented a reaction. However, no hives, bronchospasm or coagulopathy were noted.

The presence of MAOI's may have resulted in an abnormal reaction generating the entire clinical problem. It is difficult to ascertain to what extent MAOIs were involved given the variable and idiosyncratic nature of reactions in general and the patchy information available in the literature. An often reported, reaction of MAOIs in conjunction with certain narcotics is a syndrome of coma, hyperpyrexia and hypertension.^{1,2} We were unable to assess the patient's mental status because neuromuscular blockade was used to control shivering. Certainly hyperpyrexia and hypertension were present. Shivering is not usually a feature of this syndrome but was a prominent feature in this case. It may have appeared initially because the patient was hypothermic. Because this syndrome has been reported in conjunction with meperidine and not fentanyl we avoided meperidine and used fentanyl. Upon reviewing the literature (see below) we now question whether this conclusion was well founded.

If the patient's problems originated from something other than MAOIs, it is possible that their presence complicated another diagnosis and/or interfered with pharmacotherapy. The actions of MAOIs include many opposing mechanisms. In a recent review Wells *et al.*¹ listed as mechanisms of actions: reduced amine synthesis,

false neurotransmitters, increased cytoplasmic amines, presynaptic receptor inhibition, decreased number of presynaptic receptors and decreased number of postsynaptic receptors. The results may be either hypertension or hypotension. As well, abnormal responses to vasoactive agents may result. It would seem likely, therefore, that MAOIs at least complicated the management of our patient.

Discussion of literature

Reactions of patients to meperidine while on MAOIs

There are 12 case reports in the literature that implicate this combination.³⁻¹³ This "unusual reaction" results in hyperthermia, coma and usually hypertension but occasionally hypotension. In two cases, treatment with phenothiazines was thought to be effective.^{3,4} In two others, steroids were thought to be effective⁵ but in another case, steroids were not effective.¹⁰ Only one study reported giving meperidine to patients taking MAOIs in an attempt to elicit an adverse response.¹³ None of the 15 patients reacted. This suggests the "unusual reaction" is idiosyncratic and raises the issue of the frequency of the adverse event. The frequency has not been tested but the lack of response in 15 patients tested suggests it is rare.

In animals there are very different results depending on the species. In mice, morphine, pentazocine, phenazocine and meperidine all increased the LD_{50} by 40-50% when receiving MAOIs.¹⁴ Morphine has been given without effect to humans on MAOI who later reacted to meperidine.⁶ Pentazocine and phenazocine have not been associated with reactions in humans.¹⁵ In rabbits, meperidine consistently increased temperature in association with MAOIs¹⁶ but in 15 humans tested it did not.¹³ Therefore animal results from the combination of meperidine and MAOIs are very different from human results.

The mechanism of action that leads to the "unusual reaction" has been suggested to be an increase in the cerebral concentration of 5 H-T.¹⁴ This results from MAOIs but is potentiated by meperidine which blocks neuronal uptake of 5 H-T. The "unusual reaction" is thought to occur in only 20% of cases because the cerebral concentration of 5 H-T must reach a critical level.¹⁶ Animals treated with 5 H-T inhibitors do not increase cerebral 5 H-T and do not show the "unusual reaction." Unfortunately animals do not react in the same way as humans to the combination of meperidine and MAOIs (see above). Thus other authors suggest it is an idiosyncratic reaction¹⁷ and we conclude we do not understand the mechanism of action of the "unusual reaction."

Reactions of patients to fentanyl while on MAOIs

There are five cases reported where fentanyl was given to

a patient on MAOIs.^{18,19} None of these cases presented any problem. The conclusion cannot be made from these few patients that a problem does not exist. If the incidence of an idiosyncratic reaction is as rare as it appears to be with meperidine (where the advice is that we must not give meperidine to a patient taking MAOIs) we simply have insufficient data to determine if fentanyl reacts with patients receiving MAOIs.

Animal data are not helpful. One study of eight dogs found no reaction when fentanyl was given to dogs on MAOIs.* The species differences demonstrated with the meperidine data between humans, rabbits and mice bring into serious question the usefulness of the dog data.

We conclude there is simply insufficient data to help us answer the question "is fentanyl safe when patients are taking MAOIs?" Case reports describing cases with a combination of fentanyl and MAOIs should be encouraged (whether or not there is an "unusual reaction"). Certainly no one should feel comfortable with the conclusion in two recent review articles that patients on MAOIs can be given fentanyl safely.^{1,2} Those conclusions are based on inadequate information.

Reactions of patients to phenothiazines while on MAOIs
Phenothiazines have been recommended and used to treat patients with the "unusual reaction" to meperidine while receiving MAOIs^{3,4} but three fatalities have been reported with the combination of phenothiazines and MAOIs.^{20,21} One patient who died was hyperthermic and we are not told the temperature in the other two cases. The cause of these reactions is unknown and presumably rare since the combination of MAOIs and phenothiazines has been recommended in patients with psychiatric conditions.

MAOIs and inotropes

In view of the many effects of MAOIs on monoamine metabolism (e.g., epinephrine, norepinephrine, dopamine), we expect unusual results when any of these drugs are given to patients on MAOIs. But Boakes *et al.*²² found no differences in effects when NE, E, or isuprel were infused before or after MAOIs were given in four human volunteers. Phenylephrine raised BP and HR more after MAOIs than before. This is the only controlled human experiment that tests this question and the MAOI (phenelzine 15 mg tid) was only given for seven days before the inotropes were tested. The experiment can be criticised because of the small numbers of humans tested (since we are concerned about idiosyncracies with MAOI) and because the MAOI was not given for sufficient duration. Once again

we do not have sufficient data to conclude either that MAOIs should be continued or discontinued preoperatively when a procedure is undertaken that likely will include the use of inotropes.

Conclusions

That MAOIs interfere with the normal functioning of the autonomic system. Specifically they decrease catecholamine stores, change sensitivity of postsynaptic neurons and the way endogenous or exogenous monoamines are disposed of, result in unpredictable responses to CVS drugs and idiosyncratic and extreme responses to certain drugs, and idiosyncratic and extreme autonomic responses to certain stress. This, combined with the insufficient data on the use of large doses of narcotics in conjunction with MAOIs, suggests that it is logical and prudent to discontinue MAOIs before CABG surgery whenever possible.

There is little evidence to support or refute such a claim. There is some evidence to suggest that surgery that does not involve such stress on the CVS may be safe in the presence of MAOIs. However, only two case reports suggest safety for CABG surgery.

We report a case involving CABG in a patient on MAOIs that resulted in dramatic problems managing the cardiovascular system. We hypothesize that the problems would not have occurred or would have been more easily managed in the absence of the MAOI. We report a case, review the literature and conclude that there is insufficient data to suggest that CABG surgery using high-dose fentanyl in the presence of MAOIs is safe. In view of our lack of knowledge we hope other physicians who have anaesthetized patients on MAOIs will report those experiences.

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