Case Studies: Near-fatal outcome after administration of hyoscine-N-butylbromide (Buscopan®)

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Abstract
While undergoing conscious sedation for a gastroscopy, an 18-year-old female developed severe hypotension and loss of consciousness. This occurred shortly after an intravenous dose of hyoscine-N-butylbromide (Buscopan®). Resuscitation was performed over a period of 10 minutes and was successful. Once conscious, the patient complained of severe lower abdominal pain. Except for a significant metabolic acidosis (BE = -10), initial investigations were negative. She was transferred to the Intensive Care Unit (ICU) where the abdominal pain continued and the urine output was scanty for the first 12 hours. Investigations were done to exclude: anaphylaxis, mesenteric ischaemia, angioneurotic oedema, pregnancy, porphyria, autoimmune disease and myocardial ischaemia. Finally it was postulated that the drug had either caused an anaphylactoid reaction or grossly augmented cardiovagal nervous inhibition. This resulted in hypotension which caused mesenteric ischaemia that in turn resulted in severe abdominal pain and a degree of renal shutdown.

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Introduction
There have been many reports of adverse reactions to hyoscine-N-butylbromide.1-5 This case is of special interest due to the complicated differential diagnosis. Hyoscine-N-butylbromide is frequently used for gastrointestinal spasm. It is a quaternary ammonium anticholinergic agent, acting primarily on parasympathetic ganglia in the walls of the viscera.1 Here it exerts a specific antispasmodic action on smooth muscle in the gastrointestinal, biliary and urinary tracts.

Being an anticholinergic agent, all side effects and precautions cited for atropine should be applicable. Patients with glaucoma, urinary or gastrointestinal tract obstruction, unstable cardiovascular status and reflux oesophagitis should not be given this drug. This drug should be used with caution in patients with impaired metabolic, kidney and liver abnormalities.

Furthermore, side effects such as dry mouth, tachycardia, blurred vision, confusion and cognitive impairment may be a problem. Hypersensitivity reactions, particularly skin reactions, have been described.

Quaternary ammonium anticholinergic agents usually have some ganglion-blocking activity so that high doses may cause postural hypotension, but in toxic doses non-depolarising neuromuscular blockade and complete respiratory and cardiovascular collapse may be produced.1 Side effects may be increased with the simultaneous administration of other anticholinergic agents and other centrally acting drugs.

Case report
An eighteen-year-old female presented for gastroscopy. She gave no history of allergies or previous anaesthetic problems. She had received 20 mg hyoscine-N-butylbromide (Buscopan®) IV for abdominal cramps and Depo Provera IM for contraception two weeks prior to this procedure.

Her vital signs were normal; blood pressure was 100/60 mmHg and pulse 85 beats/minute. Apart from appearing extremely anxious, nothing abnormal was detected. Informed consent was obtained for conscious sedation.

Monitoring was instituted according to the recommendations of the South African Medical
A pulse oximeter and a non-invasive blood pressure device (NIBP) were connected. Oxygen was given via nasal cannulae. A 22G intravenous cannula was inserted into the dorsum of her right hand and an infusion of Lactated Ringers was initiated. The sedation consisted of: sufentanil 10 μg, midazolam 2 mg and, when the gastroenterologist was about to insert the gastroscope, 40 mg propofol was added.

Her blood pressure dropped to 85/55 mmHg and her pulse rate slowly drifted down to 48/minute and then 44/minute. The oxygen saturation (S$_{O_2}$) remained at 100% throughout. The slowing of the pulse rate did not cause concern as she was young, it was a “sleeping pulse”, and she had received an opioid and propofol.

Approximately four minutes after the start of the gastroscopy, 20 mg of hyoscine-N-butylbromide was given intravenously. At this point the pulse was 42/minute, the S$_{O_2}$ saturation 100% and the blood pressure 85/55 mmHg.

A tachycardia of 140 beats/min occurred almost immediately. The gastroenterologist commented that the gastric mucosa appeared mottled with areas of extreme blanching, indicative of severe vasoconstriction. The patient began to cough and groan. A further 20 mg propofol was given, but did not appear to sedate her. The heart rate went up to 150/minute and the NIBP monitor was “unable to record”. No peripheral pulses were present, but a weak central pulse was palpable.

The gastroscope was removed, the patient turned on to her back and an ECG monitor was immediately connected. At this point she was still breathing spontaneously, but the oximeter probe was no longer registering. The operating table was placed in Trendellenburg and the infusion of Lactated Ringers was increased to facilitate a faster flow. Cardiac massage was initiated and adrenaline was titrated in 100 μg increments. The first recordable blood pressure of 40 mmHg systolic was then measured with a manual sphygmonometer.

At this point the respiration was erratic and manual ventilation with 100% oxygen was intiated, followed by tracheal intubation and mechanical ventilation. The next blood pressure recorded by the NIBP was 60 mmHg systolic. A further 500 μg of adrenaline was titrated over 60 seconds. Her blood pressure rose to 85/50 mmHg and her pulse came down to 135/minute. She regained consciousness and pulled out her endotracheal tube. The time from administration of the drug to her extubation was nine and a half minutes.

The patient complained of severe cramp-like lower abdominal and pelvic pain. She continued to receive 100% oxygen by mask. An additional infusion of hetastarch was initiated. Gradually her vital signs stabilised as the blood pressure rose above 100 mmHg systolic and the pulse dropped below 95 beats/minute.

While still on the operating table the following tests were done:
1. A 12-lead ECG, that showed a sinus tachycardia, but no ischaemia.
2. An arterial blood gas that showed a severe metabolic acidosis with pH = 7.31, BE = -10 and HCO$_3^-$ = 18.
3. A cardiologist examined her heart and a transthoracic echocardiograph was done while the patient was still on the operating table. Her heart appeared normal.
4. A radiologist did an ultrasound of her uterus and ovaries, which also appeared normal.

She was then transferred to the ICU and monitored for the next 24 hours. She continued to complain of severe lower abdominal pain. No bowel sounds were present, but her abdomen was soft. A general surgeon was consulted to rule out the possibility of mesenteric ischaemia. When she began menstruating a gynaecologist was consulted and the β-HCG to rule out an aborting pregnancy was negative. Her urine output was relatively scanty as she passed approximately 400 ml over an eight hour period. She also complained of chest pain and this was thought to be due to the cardiac massage.

Her arterial blood gases gradually normalised. Twenty-four hours post cardiac arrest, a significant diuresis occurred. She passed 1 500 ml urine over a two hour period. She was discharged from ICU later that day.

The following blood tests were done in an attempt to determine the exact cause of the cardiovascular collapse:
a. Anaphylaxis: serum tryptase specific IgE antibodies
b. Angioneurotic oedema: C1-INH
c. Pregnancy: β-HCG
d. Autoimmune disease: antinuclear factor
e. Myocardial ischaemia: cardiac enzymes.

Urine was also tested, for porphyrins and urinary methyl histamine to exclude porphyria and anaphylaxis.

Discussion

Hyoscine-N-butyl bromide is known to cause adverse cardiovascular side effects. Anaphylaxis and...
angioneurotic oedema appear high on the list and
needed to be excluded. Although bronchocutaneous
manifestations need not be present for both these
conditions, the absence of urticaria and bronchospasm
should force the physician to include other pathologies
in the differential diagnosis.

Scopolamine has been known to markedly and
paradoxically augment cardiovagal nervous inhibition
in healthy young subjects. In this study low dose
scopolamine was postulated to decrease blood
pressure by increasing sympathetic cholinergic
outflow in the vessels of striated muscle.

After the anti-muscarinic agent was administered,
severe vasoconstriction of the gastric mucosa
occurred, as seen by the intense blanching of
the gastric mucosa. As acetyl choline normally
causes vasodilatation, it is logical to assume that
an antimuscarinic must cause some degree of
vasoconstriction. In our patient the constriction must
have been so severe that a degree of mesenteric
ischaemia occurred and probably was the cause of
her arousal prior to the gastroscope removal.

Shortly after this the blood pressure then dropped
to such an extent that she lost consciousness and
renal shutdown resulted. A severe metabolic acidosis
reflected this acute peripheral and central shutdown.

At the time of the haemodynamic collapse, the cause
was not evident and the following aethiologies had to
be excluded:

a. Abnormal cardiac anatomy, such as a left
ventricular outflow tract obstruction (HOCAM) or
aortic stenosis. This would imply that the patient
would be unable to maintain a cardiac output as
the heart rate rose significantly after the anti-
muscarinic agent. It is known that young patients
react with a greater degree of tachycardia to
all antimuscarinic agents than older patients.

b. Tachy-dysrhythmia caused a drop in cardiac
output. She did not have continuous ECG
monitoring at the time she received hyoscine.
According to the South African Medical
Association guidelines, a continuous ECG
monitor is only necessary during conscious
sedation if the patient has some cardiac
problem. The patient was a young healthy adult.

c. Hypovolaemia due to the enforced period of
starvation for eight hours prior to the gastroscope.
At the time of the cardiovascular collapse she
had received about 300 ml of Lactated Ringers.
d. A haemorrhage caused by an ectopic pregancy
or incomplete abortion causing a haemodynamic
collapse and lower abdominal pain.
e. An anaphylactoid reaction, causing a “shock”-like
picture.
f. Angioneurotic oedema. This patient had
abdominal pain, but no other oedema was evident.
Hereditary angioneurotic oedema is an autosomal
dominant state associated with the absence of
functional C1-INH. The diagnosis suggested
not only by family history but also by the lack of
urticarial reactions and the predominant signs of
gastro-intestinal attacks of colic, and episodes of
laryngeal oedema.

Transthoracic echocardiography in this patient was
normal, she had no apparent anatomical abnormality
that would make her unable to tolerate a sinus
tachycardia of 150 beats/min.

Clinically she did not appear to be dehydrated and her
reaction to the anaesthetic agents used for conscious
sedation was not consistent with that of a dehydrated
patient.

An ultrasound of her uterus and ovaries was negative;
a negative β-HCG ruled out a possible complicating
pregnancy.

In a few cases angioneurotic oedema has been
reported as a side effect of this drug. Although this
patient had severe abdominal pain, she had none of
the other signs of this condition such as urticarial skin
lesions and laryngeal oedema.

By exclusion, an anaphylactoid reaction seems the
most probable cause. However, she had none of the
other clinical signs that usually accompany these
reactions, such as bronchospasm, urticaria and
weals. It is postulated that 25% of anaphylactoid/
anaphylactic reactions do not manifest these usual
bronchocutaneous signs. Unfortunately not all of
the blood tests to investigate anaphylaxis were done
such as serum tryptase, urinary methyl histamine and
specific IgE antibodies.

Conclusion

Immediately after the administration of hyoscine
N-butylbromide, this patient presented with
cardiovascular collapse that caused a loss of
consciousness that necessitated intubation and
the use of 1 500 µg of adrenaline. She developed a
metabolic acidosis, renal shutdown and probably
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mesenteric ischaemia that persisted for eight hours post-operatively.

Blood tests to confirm an anaphylactic reaction were not done, but by exclusion the most likely cause was an anaphylactoid reaction after the administration of hyoscine N-butylbromide.

Bibliography