mitted to the epidural venous plexus, and thus explain the
forceful expulsion of blood from the needle hub seen
with coughing. From this experience, we recommend that
the stylet of the epidural needle remain in place until just
prior to aspiration and injection. This case report should
also serve to reinforce the awareness of possible VAE
during any invasive procedure in which venous integrity
may be disrupted.

REFERENCES
1. Albin MS, Babinski MF, Gilbert J, Smith SL: Venous air embolism
is not restricted to neurosurgery (letter). ANESTHESIOLOGY 50:
151, 1983
2. Lasasso TJ, Martin JD, Muzzi DA: Venous air embolism in the
recovery room producing unexplained cardiac dysrhythmias:
3. Prager MC, Gregory GA, Ascher NL, Roberts J: Massive venous
air embolism during orthotopic liver transplantation. ANES-
of venous air embolism during epidural catheter insertion.
ANESTHESIOLOGY 57:410–412, 1982

Anesthesiology

Central Anticholinergic Syndrome Following Glycopyrrolate

DANIEL F. GRUM, M.D.,* LEROY R. OSBORNE, D.O.†

The central anticholinergic syndrome (CAS) is caused
by pharmacologic substances that have anticholinergic
actions. The central and peripheral manifestations are
those of acetylcholine competitive inhibition and appear
to involve muscarinic receptors.1 Of the three muscarinic
agonists commonly used during anesthesia, atropine
sulfate and scopolamine hydrobromide are known to cause
this syndrome, whereas glycopyrrolate has not been pre-
viously reported to do so. We report a case in which gly-
copyrrolate appears to have been responsible for a par-
ticularly severe episode of CAS.

CASE REPORT

A 22-yr-old healthy woman presented in the ambulatory surgery
unit for elective diagnostic laparoscopy for pelvic pain. Her past medical

* Associate Professor.
† Resident.

Received from the University of Tennessee, Memphis, Tennessee.
Accepted for publication September 12, 1990. All work was done at
the Regional Medical Center at Memphis, an integrated hospital of the
University of Tennessee—Memphis, Memphis, Tennessee.

Address reprint requests to Dr. Grum: Department of Anesthesiol-
ogy, University of Tennessee, Memphis, 800 Madison Avenue, FG023
Chandler Building, Memphis, Tennessee 38163.

Key words: Antagonists, antimuscarinics: physostigmine. Blood-
brain barrier. Central anticholinergic syndrome. Parasympathetic ner-
vous system, premedication: glycopyrrolate.

5. Munson ES: Pathophysiology and treatment of venous air em-
bolism: A review. Middle East J Anesthesiol 9:315–325, 1988
6. Tucker WS, Jr: Symptoms and signs of syndromes associated with
Am Heart J 53:269–281, 1947
D. Body position in relation to venous air embolism: A roent-
9. Michenfelder JD, Miller RH, Gronert GA: Evaluation of an ul-
trasonic device (Doppler) for the diagnosis of venous air em-
bolism. ANESTHESIOLOGY 56:164–167, 1972
of air embolism by transesophageal echocardiography. ANES-
11. Marshall WK, Redford RF: Use of a pulmonary artery catheter
for detection and treatment of venous air embolism: A pro-
12. Hurter D, Sebel PS: Detection of venous air embolism: A clinical
report using end-tidal carbon dioxide monitoring during neu-
rosurgery. Anesthesia 34:578–582, 1979
located epidural catheters. ANESTHESIOLOGY 71:848–851,
1989

and surgical history were unremarkable except for a prior appendec-
tomy under general anesthesia without complications. She denied taking
any medications or have any allergies. She denied the acute or chronic
use of recreational drugs, alcohol, or tobacco. Family history was nega-
tive for chronic illness or drug idiosyncrasy. Her pharmacologic history
was corroborated by an accompanying family member. Upon admission
she was afebrile, had a blood pressure of 132/80 mmHg, heart rate
of 76 beats per min, and a ventilatory rate of 10 breaths per min. Her
physical exam was entirely normal. Preadmission laboratory urinalysis,
serum electrolytes, blood urea nitrogen, serum creatinine, and complete
blood count were normal.

She received 50 mg ranitidine hydrochloride intramuscularly and
30 ml 0.35 M sodium citrate by mouth. An intravenous infusion was
begun and 0.2 mg glycopyrrolate administered intravenously. Blood
pressure and heart rate remained unchanged. Ten minutes later, she
was taken to the operating room where she appeared agitated and
began to complain of a severe bilateral temporal headache. Her blood
pressure was 170/116 mmHg, heart rate 140 beats per min, and ven-
tilatory rate 20 breaths per min. One minute later these parameters
were 156/126 mmHg, 145 beats per min, and 22 breaths per min,
respectively. Five milligrams labetalol hydrochloride was administered
intravenously, but to no effect. The patient began to writhe on the
operating table and stated that her head felt like it was about to explode.
Upon her complaint that the operating room was too bright, it was
noted that her pupils were widely dilated. Her skin was hot and dry
and her oral mucosa was dry. She denied ever having had a similar
experience.

A presumptive diagnosis of CAS was made, and 1 mg physostigmine
was administered intravenously. Three minutes later the patient was
much less agitated and related a marked decrease in the severity of
her headache. Blood pressure was now 151/109 mmHg, heart rate
138 beats per min, and ventilatory rate 16 breaths per min. A second
injection of 1 mg physostigmine given 10 min after the first calmed
the patient and relieved her of her headache. Her blood pressure was
141/91 mmHg, heart rate 91 beats per min, and ventilatory rate 16
breaths per min. Surgery was cancelled and the patient transported to
the recovery room. Ten minutes after the second dose of physostigmine,
hers blood pressure was 150/77 mmHg, heart rate 66 beats per min,
and ventilatory rate 14 breaths per min. She was resting quietly and
was totally free of any headache, although she complained of nausea
for several minutes.

A 12-lead electrocardiogram revealed a sinus bradycardia and ven-
tricular trigeminy, with a nonconducted P-wave following each pre-
mature ventricular complex. This rhythm persisted for 30 min and
was succeeded by a sinus rhythm with frequent premature ventricular
complexes for the next 4 h. She remained asymptomatic, and her elec-
trocardiogram reverted to normal by the following morning. Serum
electrolytes, blood urea nitrogen, and serum creatinine drawn during
the acute event and the following evening were normal. She was dis-
charged on the following day and was to be readmitted later in the
week for laparoscopy.

A serum toxicology screen was drawn during the acute event and
evidence for the following drugs sought (the sensitivities of the indi-
vidual drug analyses are in parentheses): amphetamines (0.09 µg/ml),
barbiturates (0.06 µg/ml), cocaine metabolites (0.03 µg/ml), phen-
cyclidine (5.0 ng/ml), opiates (25 ng/ml), and benzodiazepines (40
ng/ml). This serum screen was entirely negative, as was a urine toxi-
cology screen for common substances or their metabolites.

DISCUSSION

To our knowledge, this is the first reported case of
severe acute CAS following administration of glycopyr-
rolate. The manifestations of the syndrome are the per-
ipheral and central effects of competitive inhibition of
acetylcholine. Of the antimuscarinic agents commonly
used in anesthetic practice, the tertiary amines atropine
sulfate and scopolamine hydrobromide cross the blood–
brain barrier and have notable, though dissimilar, central
nervous system effects. Glycopyrrolate, chemically a quan-
ternary ammonium compound, is less lipid-soluble than
the tertiary amines, and therefore its passage across the
blood–brain barrier is relatively more limited. Although
drowsiness has been noted following administration, gly-
copyrrolate is usually listed as being devoid of central
nervous system effects. Since this patient did not have any medical condition
that could have altered her blood–brain barrier and its
permeability to glycopyrrolate, that drug most likely did
not have a central effect. However, it is unlikely that any
drug other than glycopyrrolate was responsible for this
patient’s acute symptomatology. Sodium citrate is an alkali-
zation agent, acts similar to bicarbonate when absorbed,
and certainly is devoid of antimuscarinic effects. Raniti-
dine, an H2-receptor blocker, has been associated with
severe headaches and rarely with arrhythmias. However,
the dry skin and mouth, dilated pupils, photophobia and
severely elevated diastolic blood pressure experienced by
this patient do not coincide with the probable result of
unopposed H2-receptor-mediated effects.

Cocaine is the most common pharmacologic cause of
severe cardiovascular toxicity in patients admitted to our
institution. Cocaine readily diffuses across the blood–brain
barrier and concentrates in central nervous system tissue. In
addition to the increase in cardiac rate probably caused
by stimulation of the central nervous system in general,
cocaine may produce a prominent rise in blood pressure
secondary to tachycardia and sympathetically mediated
vasoconstriction. Cocaine produces these effects by pre-
venting neuronal uptake of norepinephrine after its re-
lease. Cocaine also has a micromolar affinity for muscarinic
receptors and has been listed as one of the causes of
CAS. Central nervous system symptoms result either
from potentiation of catecholamine activity or from
depression of central inhibitory pathways. The lack of
history or physical evidence of drug abuse and the nega-
tive acute serum and urine toxicologic screens argue
against cocaine as the cause of this patient’s symptoms.

There are several possible explanations for the electro-
cardiographic abnormalities in this patient. Labetalol,
in addition to its beta-blocking effect, which accounts for
a decrease in heart rate, stabilizes membranes similarly
to local anesthetics. Physostigmine can cause bradycardia
and even asystole. Either drug may account for the
bradycardia, and their interaction may account for the
nonconducted atrial activity.

In summary, a healthy young adult patient developed
manifestations of CAS. Although previously unreported
in the literature, the probable cause was glycopyrrolate.
The manifestations were promptly and effectively reversed
by physostigmine. In view of the large number of drugs that have the potential to cause this syndrome, it
is surprising that CAS does not occur more often. Its oc-
currence in a patient who received a drug not believed
to cause CAS illustrates the continuing need to maintain
a high level of awareness of its presentation and to con-
sider it in the differential diagnosis of patients having an
acute onset of neurologic and cardiovascular symptoms.

REFERENCES

1. Flacke WE, Flacke JW: Cholinergic and anticholinergic agents,
Drug Interactions in Anesthesia. Edited by Smith NT, Corbascio
2. Mirakhur RK, Dundee JW, Jones CJ: The evaluation of anticholi-
ergic actions of glycopyrrrolate bromide. Br J Clin Pharmacol
5:77–84, 1978
3. McCubbin TD, Brown JH, Dewar MS, Jones CJ, Spence AA: Gly-
copyrrrolate as a premedicant: Comparison with atropine. Br J
Anaesth 51:885–889, 1979
1979
5. Durrett LR, Lawon NW: Autonomic nervous system physiology
and pharmacology, Clinical Anesthesia. Edited by Barash PG,
Cullen BF, Stoetting RK. Philadelphia, JB Lippincott, 1989, pp
105–226
7. Ellenhorn MJ, Barceloux DG: Medical Toxicology: Diagnosis and
Intraoperative Subdural Tension Pneumocephalus Arising after Opening of the Dura

DAVID GOODIE, M.B., B.S.,* ROGER TRAILL, M.B., B.S., F.F.A.R.A.C.S.†

Perioperative tension pneumocephalus was first described byECTORS1 in 1962 and has been described many times since.2-11 It has, however, never been reported as occurring intraoperatively in the subdural space when the dura is open. We describe two cases in which subdural tension pneumocephalus occurred during craniotomy after dural opening. Both of these presented as acute, severe brain swelling of unknown etiology.

REPORT OF TWO CASES

Case 1. A previously healthy 63-yr-old, 71-kg woman presented with a 6-month history of increasingly frequent frontal headaches. Clinical examination revealed mild bilateral papiledema and an ataxic gait. A computerized tomography (CT) scan demonstrated a right-sided lesion, enhanced with contrast, that was adjacent to and obstructing the third ventricle. A magnetic resonance imaging (MRI) scan suggested a vascular malformation.

The patient was scheduled for a bifrontal craniotomy in the supine position. Preoperatively, dexamethasone (Decadron® 4 mg four times per day), ranitidine (150 mg two times per day), and phenytoin (300 mg/day) were given. All laboratory data were within normal limits. Blood pressure was 130/80 mmHg. No additional aortic or pulmonary medication was prescribed.

Anesthesia was induced with thiopental 300 mg and fentanyl 400 μg, and the trachea was intubated after vecuronium 10 mg. Anesthesia was maintained with N2O 70% in O2 and the arterial hemoglobin O2 saturation (SPO2) kept between 96-98%. Throughout surgery, core body temperature, intratraumatic blood pressure, central venous pressure, end-tidal CO2 partial pressure (PETCO2), neuromuscular blockade, and breath sounds were continuously monitored. Ventilation was controlled to maintain an PETCO2 of 27 mmHg.

The head was placed in the neutral position and immobilized in Mayfield pins. Mannitol 100 g and furosemide 20 mg were administered. A diuresis of 2,100 ml had occurred by the time the dura was opened (90 min after diuretics). Prior to incision, an additional 300 μg fentanyl was administered. Trimetaphan was used to maintain the systolic blood pressure between 100 and 120 mmHg intraoperatively. A bifrontal craniotomy was performed, and the dura was opened over the right hemisphere adjacent to the falx cerebri.

Initially the brain was quite shrunken, but 30 min later it began to swell, and increased venous bleeding developed. No change in physiologic parameters had occurred, and the breathing circuit was not obstructed. A surgical cause of the swelling was suggested; however, on palpating the intact dura over the left hemisphere, the surgeon believed that "a subdural hemorrhage was unlikely."

Surgery proceeded, and the right hemisphere was gently retracted to gain access to the lesion. As the sucker was applied along the right side of the falx cerebri to evacuate clot, air under pressure was suddenly released through an aperture in the falx. This was followed by a prompt resolution of the swelling and bleeding. It appeared that subdural air had collected over the left hemisphere and that blood had sealed its point of entry.

No further complication was encountered, and a cavernous hemangioma was excised. The patient made an uneventful recovery.

Case 2. A 26-yr-old, 64-kg woman presented with a 3-week history of right-sided weakness and mild motor dysphasia. Clinical examination revealed mild weakness and hyperrelexia in both the right upper and right lower limbs and early bilateral papilledema. A MRI scan identified multiple areas of altered signal intensity throughout the left cerebral hemisphere, suggestive of metastases. No primary lesion could be identified, and the patient was scheduled for an open biopsy through a left parietal craniotomy in the semi-sitting position. Laboratory data were within normal limits. Dexamethasone (Decadron® 4 mg four times per day), ranitidine (150 mg two times per day), and phenytoin (300 mg/day) were given preoperatively.

The patient received temazepam 20 mg orally. After the monitoring (as in Case 1) was established, anesthesia was induced with thiopental 300 mg and fentanyl 500 μg, and after vecuronium 10 mg was given, the trachea was intubated. Anesthesia was maintained with 70% N2O in O2 while the Spo2 was kept between 95-97% and the lungs ventilated to an PETCO2 of 26 mmHg.

The head was immobilized, brow uppermost, in Mayfield pins and elevated to 20 cm above the heart. At the same time, mannitol 75 g and furosemide 20 mg were administered, and 2,500 ml urine was produced by the time the dura was opened (100 min after diuretics). Prior to dural incision the brain was noted to be shrunken. The dura was opened over the left parietal lobe adjacent to the falx cerebri. Almost immediately the brain began to protrude into the craniotomy and by 15 min had swollen to an alarming degree. A rapid appraisal of the anesthetic technique (as for the previous case) was unable to