Clinical Reports

Opisthotonos following propofol: a nonepileptic perspective and treatment strategy

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In this report of opisthotonos during recovery from propofol anaesthesia, we relate clinical observations with scientific considerations, and propose a strategy for treatment of this rare side effect. Following a brief operative procedure, a healthy 29-yr-old woman developed recurrent opisthotonos while recovering from anaesthesia with alfentanil, propofol, and nitrous oxide. In contrast to accumulating reports, the patient remained conscious during each episode of back extension and retrocollis. The preservation of consciousness and similarities to strychnine-induced opisthotonos suggest to us that the mechanism may have a brainstem and spinal origin. Recent investigations show that propofol potentiates the inhibitory transmitters glycine and γ-aminobutyric acid (GABA) which would enhance spinal inhibition during anaesthesia. Postanaesthetic opisthotonos, however, may be due to a propofol-induced tolerance to inhibitory transmitters. This rebound phenomenon would lead to an acute, enduring refractoriness in inhibitory pathways of the brainstem and spinal cord, resulting in increased activity of extensor motoneurons. We recommend a therapeutic strategy that restores inhibition by glycine and GABA at multiple sites; the preferred therapeutic agents would be diazepam and physostigmine. The episodes are usually short-lived, but two of the reviewed 17 patients developed recurrent retrocollis for four and 23 days following antiepileptic drug therapy. Since high doses of phenytoin and carbamazepine can result in opisthotonos, we recommend that anticonvulsants be reserved for post-anaesthetic patients with electroencephalographic evidence of seizure activity.

Dans ce rapport d'opisthotonos survenant au cours du réveil d'une anesthésie réalisée au propofol, nous décrivons les observations cliniques avec leurs considérations scientifiques, et proposons une stratégie de traitement de cet effet inusité. Après une chirurgie brève, une patiente de 29 ans, en bonne santé, développe un opisthonos récurrent alors qu'elle se réveille d'une anesthésie réalisée avec alfentanil, propofol et protoxyde d'azote. Contrairement aux observations accumulées, elle reste consciente à chaque épisode d'extension dorsale et cervicale. La persistence de la conscience ainsi que la similitude de cet opisthonos avec celui induit par la strychnine nous suggère que le mécanisme peut avoir son origine du tronc cérébral et de la moelle. Des investigations récentes montrent que le propofol potentialise la glycine et l'acide γ-aminobutyrique (GABA), neurotransmetteurs inhibiteurs, ce qui pourrait accentuer l'inhibition médullaire pendant l'anesthésie. L'opisthonos postanesthésique peut être secondaire à une tolérance aux transmetteurs inhibiteurs induite par le propofol. Ces phénomènes de rebond pourraient conduire à une résistance aiguë et durable aux influx inhibiteurs du tronc cérébral et de la moelle, résultant en une activité accrue des motoneurones extenseurs. Nous recommandons une stratégie thérapeutique qui restaure l'inhibition de la glycine et du GABA à des sites multiples: les agents thérapeutiques de choix seraient le diazepam et la physostigmine. Les épisodes sont habituellement brefs, mais deux des 17 patients revus ont développé une extension du cou récurrente à quatre et 23 jours après un traitement antiépileptique. Puisque des doses élevées et phénytoïne et de carbamazépine peuvent entraîner un opisthonos, nous recommandons que les anticonvulsivants soient réservés aux patients qui présentent une activité comitiale à l'électroencéphalogramme après leur anesthésie.

Key words
ANAESTHETICS, INTRAVENOUS: propofol;
COMPLICATIONS: decerebrate rigidity, opisthotonos;
PHARMACODYNAMICS: tolerance;
RECEPTOR: glycine, GABA.

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We present a patient who developed opisthotonos while recovering from anaesthesia with alfentanil, propofol, and nitrous oxide. In contrast to previous reports,[1-14] the patient described here remained conscious during recurrent retrocollis with extension of trunk and arms, implying compromised spinal inhibition. Opisthotonos occurs rarely as a pharmacological side effect of many drugs, particularly in overdose. We address whether propofol-induced opisthotonos is an epileptic disorder (cf. recent editorial[15]), and propose a strategy to re-establish spinal inhibition.

Case report

A 29-yr-old woman presented for cervical dilatation and curettage following a miscarriage in the first trimester of pregnancy. The patient was otherwise healthy with no history of an epileptic disorder. Without premedication, she received alfentanil (1400 μg), d-tubocurarine (3 mg), propofol (120 mg) and succinylcholine (100 mg). Following tracheal intubation, anaesthesia was maintained for ten minutes with nitrous oxide and four bolus injections of propofol (20–30 mg). The patient then regained consciousness and the trachea was extubated. She moved herself from the operating table to the stretcher, and talked during transfer to the postanaesthetic care unit.

Shortly after arriving in the recovery facility, the patient suddenly extended her arms, and bent her head and back posteriorly. At the same time, with clenched teeth, she stopped breathing for 30 sec. The patient was aware and frightened, partly because of the brief inability to breathe. Over the next 75 min, opisthotonos recurred every three to five minutes, despite injections of diazepam (2.5 mg, three-times *iv*) and diphenhydramine (25 mg, twice *iv*). However, the intensity, duration, and frequency of retrocollis gradually decreased. During each episode the patient remained conscious, but was unable to speak and had great difficulty in initiating voluntary movement.

Discussion

Opisthotonos is a tetanic disorder where the spine and extremities are hyper-extended. The back and neck bend posteriorly with convexity forward. Classically, the patient is awake and the body rests on the head and heels.

Propofol-induced opisthotonos

Although the incidence of opisthotonos may be as high as 2.7% in dogs,[16] severe excitatory events are rare in patients receiving propofol.[15] There are, however, many accumulating reports of tonic-clonic movements of the extremities with or without opisthotonos as a consequence of propofol administration. Because of an uncertain relationship of the movements to the mechanism of retrocollis, we have not included these reports unless there was an associated extension of the head and neck.

The MEDLINE® database contains 17 reports of propofol-induced opisthotonos.[1-14] In most cases, the patient received propofol in combination with other drugs, such as fentanyl or alfentanil,[2-8] and in two cases as the sole agent.[1,14] Since three female patients had either personal[3,5] or family[12] histories of epileptic disorders (prevalence of only 0.13%), investigators suggested that propofol may have a convulsant property[5,11] and should not be administered to women with epilepsy.[13] There is little experimental evidence, however, that propofol induces or facilitates the genesis of seizures.[17,18]

We searched the propofol cases for clues that would implicate opisthotonos. The reports have a female-to-male ratio of about 3:1, with three cases that occurred briefly on induction of propofol anaesthesia,[1,2,8] and 14 cases on recovery. In the postoperative group, the opisthotonos usually took place during the first hour, but in one case it occurred six hours after anaesthesia.[13] Before developing opisthotonos in the postoperative period, some patients recovered consciousness as expected, whereas others had prodromal signs that included unconsciousness,[4,6] restlessness,[3-5,11] grimacing,[6,10] and nystagmus.[4] Sensory stimulation sometimes triggered the onset of a brief opisthotonos[4,5] with or without apnoea[14] and tonic-clonic movements.[7-13] Opisthotonos invariably recurred every few minutes in the postanaesthetic group, but usually lasted less than an hour. In two of the 16 patients, however, episodes of opisthotonos continued for four[7] and 23[10] days. In a third patient, episodic tonic-clonic movements persisted for seven days following opisthotonos.[12]

Several other anaesthetic agents,[19] including nitrous oxide,[20,21] alcohol,[22] benzodiazepines,[23] ketamine,[24] phencyclidine,[25] and epidural morphine,[26] can produce opisthotonos. Experimentally, Althesin®[27] and isoflurane[28] anaesthesia can result in opisthotonos. Retrocollis occurs either on anaesthetic induction or recovery. In the reports on alcohol and benzodiazepines, however, extensor episodes developed as a rebound phenomenon following chronic drug use.

What conclusions can we infer from these reports? Opisthotonos can occur as a long-lasting side effect of many different anaesthetics and may resemble a withdrawal reaction, occasionally with some preservation of consciousness.[23] In our patient, the maintenance of consciousness suggests to us that the mechanism may be primarily spinal.[5]

Previous treatment of propofol-induced opisthotonos

In some instances, clinicians have treated this disorder as an extrapyramidal side effect or a drug-induced seizure. However, centrally acting anticholinergics[6,7,9,11] appeared

to have no effect, and propofol,[11] thiopentone,[3,11] or benzodiazepines[7,9,10] only briefly stopped the episodes. Repeated administration of propofol may have exacerbated the recurrent pattern.[11] The therapeutic failures led investigators to suggest alternative diagnoses, such as hysteria[9] or side effects from hypothetical long-lasting metabolites of propofol.[5,11] A glucuronide conjugate is the major, long-lasting metabolite of propofol in humans.[29] Unlike morphine glucuronides, propofol glucuronide is apparently inactive.

Does antiepileptic drug therapy aggravate the opisthotonos? We draw attention to the two patients, noted above, who developed recurrent retrocollis for four and 23 days. Administration of valproate[7] or phenytoin,[10] in multiple doses, did not stop the opisthotonos. Similarly, in the patient with tonic-clonic movements lasting for seven days, administration of phenytoin and valproate did not halt the excitatory episodes. Since the two epileptic patients[3,5] were taking carbamazepine before they developed retrocollis, we suggest that attention may be more appropriately placed on a drug interaction than on preexisting epilepsy or theoretical convulsant properties of propofol. It may be relevant that an anticholinesterase agent with convulsant properties (physostigmine[19]) and a new sedative, chlormethiazole,[6] stopped the opisthotonos.

Decerebrate rigidity

The neurophysiological basis of opisthotonos involves decerebrate rigidity[4] and the antigravity muscles, without obligatory loss of consciousness.[30] Midbrain lesions mimic this situation by releasing the reticular formation and spinal cord from cortical inhibition.[31] Extensor muscle tone predominates in patients with lesions because neurogenic activity drives the antigravity muscles more strongly than the flexor muscles. Normally, postural muscle activity is regulated by inhibitory pathways in the brainstem and spinal cord that use glycine (glycinergic) and γ-aminobutyric acid (GABA or GABAergic) as transmitters. Compromised inhibition in the brain and spinal cord due to lesions or drug actions can lead to decerebrate rigidity and opisthotonos.

GABAergic and glycinergic pathways

Lesions and drugs can decrease the GABAergic output of the cerebellum, i.e., the inhibitory activities of the Purkinje cells. This releases brainstem control of motoneuronal activity in the spinal cord, and therefore increases extensor muscle tone.[31,32] Drugs like strychnine and tetanus toxin produce decerebrate rigidity by reducing transmission by glycinergic interneurons in the spinal cord.[33] The axons of spinal motoneurons have recurrent, cholinergic collaterals that excite glycinergic (inhibitory) interneurons, called Renshaw cells (see Figure). Tetanus

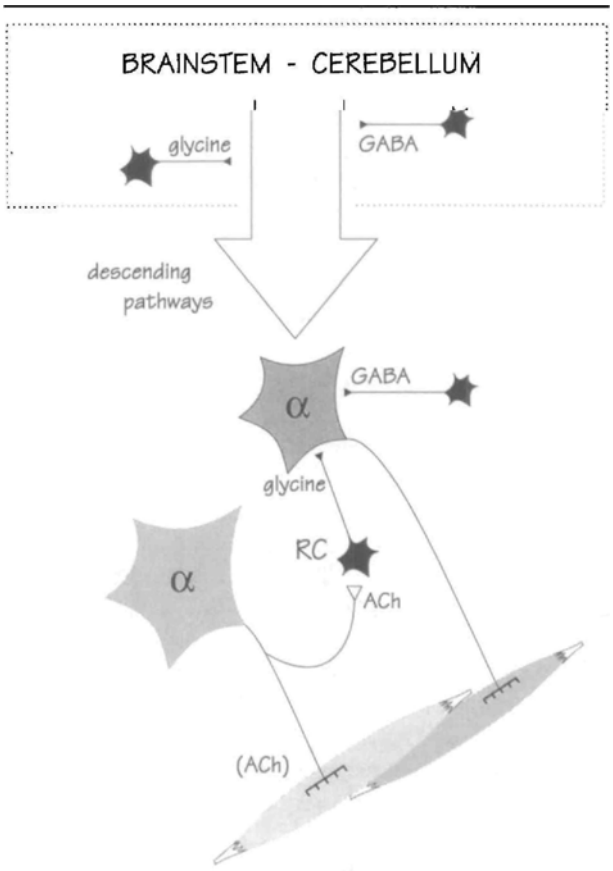

FIGURE The control of activity in spinal motoneurons (α) involves the integrities of inhibitory pathways that use glycine and GABA as transmitters (black neurons). Within the cord, motoneurons send recurrent collaterals to inhibitory interneurons called Renshaw cells (RC) that release glycine on motoneurons. The excitatory transmitter at the motoneuron-Renshaw cell synapse is acetylcholine (ACh). Spinal interneurons that release GABA also produce inhibition of motoneurons.

toxin suppresses the release of glycine from interneurons, including Renshaw cells, which, in turn, exaggerate the activities of motoneurons, resulting in tetanus dorsalis (opisthotonos). Strychnine has the same effect by antagonizing the postsynaptic receptors for glycine. Sensory stimulation of patients with strychnine poisoning evokes episodes of retrocollis and compromised respiratory movements, without loss of consciousness.[34] These characteristics are consistent with our observations, and suggest to us a spinal mechanism involving glycinergic pathways for propofol-induced opisthotonos.

Proposed mechanism

A strychnine-like antagonism of glycinergic inhibition by propofol[35] would be expected to produce opisthotonos during maintenance, and not on discontinuation of the anaesthesia. Recent investigations, however, show that

propofol potentiates glycinergic[36,37] and GABAergic transmission,[38] which would increase descending inhibition to the spinal segments during anaesthesia.

In the recovery phase following propofol anaesthesia, opisthotonos may be due to a rebound mechanism involving compromised inhibition in the brain and spinal cord. During propofol administration, an acute tolerance to inhibitory transmitters may lead to a refractoriness in glycinergic[39] and GABAergic[40] pathways in brainstem and spinal levels, which continues following propofol elimination. The decreased inhibition of spinal cord output would result in overwhelming extensor muscle tone, viewed clinically as opisthotonos.

The removal of inhibition in supraspinal neurons with GABAergic inputs could explain the rapid emergence and euphoria following propofol anaesthesia. Antagonists of the $GABA_A$ receptor subtype are convulsants, and a refractoriness to GABA[41] may account for the tonic-clonic movements following propofol administration.

Concerns about antiepileptic drugs

In support of the possible aggravation of propofol-induced opisthotonos by anticonvulsant therapy, phenytoin[42] or carbamazepine[43] overdose in humans can produce recurrent opisthotonos. The original observations of toxic phenytoin doses producing retrocollis in experimental animals, however, are even more suggestive.[44] In these studies with very high doses, the investigators reported that phenytoin produces an initial CNS depression, and then opisthotonos during recovery. Furthermore, a side effect of high phenytoin doses in humans – cerebellar degeneration[45] – may be relevant to the long-lasting propofol-induced opisthotonos in the patients treated with antiepileptic drugs.[7,10] In addition, direct actions of phenytoin on GABAergic systems[46–48] and spinal reflexes[49] would exaggerate the output of the spinal cord. From several perspectives, therefore, anticonvulsants can aggravate postanaesthetic opisthotonos.

Therapeutic considerations

Clinicians may prefer, conservatively, to withhold propofol and use thiopentone in patients with a previous history of anaesthetic-induced opisthotonos,[9] and in patients taking carbamazepine, phenytoin, or valproate. During recovery from propofol anaesthesia, warning signs may include anxiety, restlessness, grimacing, nystagmus, and delayed recovery of consciousness. In this situation, excessive tactile or other sensory stimulation should be avoided.[4] Reassurance may be facilitated by light sedation with a long-acting benzodiazepine (e.g., 1–3 mg diazepam *iv*).

Specific treatment of opisthotonos should be aimed at potentiating glycinergic and GABAergic transmission. As above, small doses of diazepam may be effective because of its ability to potentiate activity at $GABA_A$ receptors.[38] Additionally, physostigmine (e.g., 1 mg *iv*) may restore spinal inhibition by stimulating Renshaw cell inhibition of motoneurons. Chlormethiazole, which potentiates both glycinergic and GABAergic transmission,[50] and the experimental glycine agonist, MDL 27,531,[51] may be useful in the future treatment. Also worthy considerations include the use of baclofen, an orally effective antispastic agent because of its $GABA_B$ agonist properties,[52] and hydrocortisone, which may potentiate glycine actions.[53]

Considering this possible mechanism, propofol should not be used to treat opisthotonos or epileptiform movements. Similarly, morphine or fentanyl (or congeners) could aggravate propofol-induced opisthotonos because opioids can antagonize glycine actions.[33] Until the specific proposals are investigated, we would avoid using antiepileptic drugs in the treatment of patients experiencing anaesthetic-induced opisthotonos or "seizure-like" movements. Patients with epileptiform movements should be treated with benzodiazepines before electroencephalographic examination.

In conclusion, we propose that postanaesthetic opisthotonos is due to an acute, enduring refractoriness in inhibitory pathways of the cerebellum, brainstem, and spinal cord. This also may account for tonic-clonic movements during recovery from propofol anaesthesia. We would not prejudice treatment of opisthotonos as an epileptic disorder. Until the completion of systematic studies in a laboratory setting, we recommend the avoidance of antiepileptic drug therapy and a therapeutic strategy that accentuates glycinergic and GABAergic inhibition at multiple sites in the brainstem and spinal cord.

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