Psychotic Reaction Associated with Postpartum Use of Indomethacin

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INTRODUCTION

Indomethacin, like other nonsteroidal anti-inflammatory drugs, exhibits anti-inflammatory, analgesic, and antipyretic properties and is therefore used to treat acute and chronic pain. The mechanism by which nonsteroidal anti-inflammatory drugs produce these effects is not fully understood; however, it is believed to be related to the inhibition of cyclooxygenase, an enzyme that catalyzes the formation of prostaglandins.[1] Prostaglandins (for example, bradykinin) are thought to sensitize pain receptors to mechanical or chemical stimulation.[1] In gynecologic and obstetric applications, nonsteroidal anti-inflammatory drugs are useful for treating various pain syndromes thought to result from an increase in serum prostaglandins, such as dysmenorrhea, uterine contractions, and premenstrual physical complaints (back and muscle aches, headache, breast tenderness, and gastrointestinal discomfort).

Thirty to sixty percent of patients receiving indomethacin report adverse effects, most involving the central nervous and gastrointestinal systems.[1] This report describes a psychotic reaction in a patient who received an indomethacin suppository postpartum.

CASE REPORT

A 36-year-old woman received an indomethacin suppository 100 mg rectally 2 days postpartum for relief of pain; the birth had been by cesarean section performed with spinal anesthetic. The suppository was administered at 2005. At 2050 she reported dizziness and required assistance to go to the washroom. She stated that she was very hot, sweaty, and nauseated and that her heart rate was higher than normal. She also stated that her mind was racing and that although she was well aware of what she was doing and saying, she had no control over herself or her thoughts. She remained seated on the toilet for 2 h, unwilling to move to the bed. During this period, she rocked constantly, picked at herself, wrung her hands, and stated that she was "going crazy". She felt unable to close her eyes. She did not want to be left alone, and her husband was called to sit with her. A single set of vital signs taken at the onset of the episode were as follows: temperature 36.2°C, pulse 108 beats/min, and blood pressure 104/60 mm Hg.

The reaction began to abate approximately 3 h after the suppository was administered, and by 4 h after administration it had completely resolved. Other causes of the reaction were not apparent. The patient had received acetaminophen 325 mg with codeine 30 mg (5 doses, last dose taken at 1600) and ibuprofen 400 mg (2 doses, last dose taken at 1600), but she had tolerated these drugs previously, and she subsequently received and tolerated them. No other pain medication was administered with the indomethacin suppository, and no similar reaction occurred when the patient received acetaminophen 325 mg with codeine 30 mg or ibuprofen for pain. There was no history of adverse drug reactions with nonsteroidal anti-inflammatory drugs, although previous drugs of this type had been taken orally. The patient was previously completely healthy and had no history of mental illness or substance abuse. Because of the severity of the reaction, the medication was not reintroduced. No sequelae were noted after 8 months' follow-up, although she took other nonsteroidal anti-inflammatory drugs (specifically ibuprofen) orally after this event.

DISCUSSION

Indomethacin is a commonly prescribed analgesic used extensively in gynecologic and obstetric patients. Indomethacin-associated adverse effects on the central nervous system are common (headache in 10% to 50%

of patients, dizziness in 3% to 9%, depression or fatigue in 1% to 3%).[1] Psychiatric disturbances including psychotic reactions are less common (less than 1% of patients)[1]; however, there have been several reports of patients experiencing psychotic-type reactions while taking indomethacin (Table 1). Of the cases reported previously, all involved patients (38 to 92 years of age) receiving oral therapy.[2–10] Only one patient had a history of psychiatric disease.[8] The dosage ranged from 75 to 200 mg per day. Symptoms included combativeness, hostility, hallucinations, paranoia, confusion, disorientation, and depersonalization. Treatment included withdrawal of indomethacin and a short course of chlorpromazine 100 mg/day, haloperidol 0.5 to 5 mg daily, or diazepam 5 mg/day. There were no reports of young female patients receiving the drug postpartum and experiencing these types of reactions.

The mechanism by which indomethacin produces acute psychosis is not known. One suggestion is that indomethacin may be similar in molecular structure to serotonin.[11] Both indomethacin and serotonin have an indolic moiety that may be related to the development of acute psychosis.[11,12] In postpartum patients, a hormonal mechanism may be responsible for the psychotic effect. The rate of absorption of indomethacin after rectal administration of suppositories has generally been reported as more rapid than after oral administration of conventional capsules.[1] The rapid absorption of the drug by the rectal route may cause severe dizziness, but this does not fully explain the psychotic-like episode.

The patient described here received a relatively high dose of indomethacin (100 mg), which may help to explain the psychotic reaction. However, a review of charts for December 1998 to December 1999 revealed that this dose is standard for postpartum patients at this particular institution.

The patient had received spinal anesthetic for the cesarean section, but this procedure had been performed 48 h before the psychotic-like event. The anesthetic (hyperbaric bupivacaine 0.75% [1.6 mL]) was used for only a short period and could not have contributed to the event. No medications other than those previously described had been taken.

Indomethacin is distributed into breast milk.[1] Seizures occurred in a 6-day-old neonate who was being breast-fed and whose mother had taken approximately 200 mg of indomethacin daily for about 3 days.[1] Because of the potential for indomethacin to cause adverse effects in infants and the availability of many alternative pain medications, a decision must be made as to whether the risks of using this agent postpartum outweigh the benefits.

The frequency of this reaction in postpartum patients is not known. No cases of psychotic reactions occurring in young postpartum women have been reported previously. However, an informal survey of postpartum nursing staff and obstetricians suggested that such reactions are certainly not rare and are likely underreported. As a result, many of our obstetric and anesthesia staff have voluntarily stopped prescribing this agent for postpartum use.

Table 1. Published Reports of Indomethacin-Induced Psychosis

Reference	Age (years)	Sex	Underlying Disease	Dosage and No. of Doses	Psychiatric Symptoms
Carney (1977)[2]	55	F	Rheumatoid arthritis	100–150 mg/day (6 doses)	Paranoid delusions, olfactory and visual hallucinations
Gotz (1978)[3]	80	F	Pseudogout	25 mg tid (1 dose)	Verbal hostility, hallucinations, paranoia
Tollefson and Garvey (1982)[4]	83	F	Acute gouty arthritis	50 mg tid (12 doses)	Agitation, delusions
Schwartz and Moura (1983)[5]	63	F	Gout	50 mg tid (2 doses)	Depersonalization, feelings of disorientation, anxiety, depression
Bishop et al. (1987)[6]	45	F	Arthritis	50 mg bid (4 doses)	Mania, anxiety, panic attacks
Oron et al. (1992)[7]	47	M	Reiter's syndrome	25 mg (1 dose)	Visual hallucinations, agitation, delirium
Bessa (1994)[8]	71	F	Acute gout	200 mg daily (3 days)	Hallucinations and paranoid ideas
Lear and Moore (1994)[9]	38	M	Arthritis	50 mg bid (60 doses)	Depersonalization, agitation
Mallet and Kuyumijian (1998)[10]	92	M	Pseudogout	25 mg tid (6 doses)	Agitation, aggression

According to the scale of Naranjo and others[13] for determining the probability that an adverse reaction is related to a particular drug, the adverse event reported here was probably related to indomethacin (score 6 out of a possible 10 points for this patient).

The emotional and physical distress that an acute psychotic episode causes to patients and their families, particularly in the postpartum period when neonatal bonding is occurring, suggests that health-care providers should rethink the use of indomethacin. Given that indomethacin is distributed in breast milk, alternative pain therapies should be considered, particularly in lactating mothers. Further study is needed to fully document the prevalence of this disturbing adverse reaction.

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