Droperidol: Efficacy and Side Effects in Psychiatric Emergencies

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Background: As admission criteria to inpatient units become more focused on patient safety and behavioral instability, primary treatment often requires use of medications that need to be quick, safe, and effective for control of agitation. This article reviews the evidence that droperidol may serve as the optimal medication for this task.

Data Sources: A comprehensive MEDLINE search of English-language literature was conducted using the search term *droperidol* concerning the use of droperidol in psychiatric emergencies. Cross-referencing of those articles was conducted to include pertinent articles in the nonpsychiatric and European literature regarding safety and early development of the drug.

Study Findings: As evidenced in the animal and clinical literature, studies demonstrate the efficacy and rapidity of onset of droperidol and its relative safety compared with the most widely used antiagitation drug, haloperidol. Evidence for this use of droperidol is particularly compelling for situations in which intramuscular administration is necessary.

Conclusion: Droperidol, while not in widespread use, may prove to be the superior typical neuroleptic for psychiatric emergencies. Increased clinical utilization and study of droperidol for this use is warranted.

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The goals of psychiatric hospitalization have changed drastically in the last quarter century as a product of the deinstitutionalization movement, and more recently from the effects of managed care. While the length of psychiatric hospitalization continues to decrease, the criteria for psychiatric admissions have become more stringent. Admissions evaluations are therefore increasingly founded on a determination of grave disability or a risk of violence by patients to themselves or others. Modern psychiatric hospitalization has thus become what used to be regarded as "intensive care" psychiatry, the goal of which is to treat and protect patients from the potential for violence of some form. One may predict that inpatient units would have an increasing incidence of dangerous behavior as a result of this trend. Indeed, there are reports of increasing rates of violent incidents and staff injuries on psychiatric wards.[1] Snyder[2] examined the effects of hospital downsizing on rates of assaults in the inpatient setting. At a large Maryland state hospital, there was a rate of 5.5 assaultive injuries per 100 patients in 1980 and 50.5 per 100 patients in 1989.[2] At the same institution over the time period, a reduction in census was seen without a proportional change in admission rate, resulting in a larger proportion of patients who were severely ill. Corresponding to this finding are reports that indicate that injury rates for psychiatric nursing staff are now higher than injury rates seen in work settings more traditionally associated with physical risk, such as mining, lumber, and heavy construction.[3] In the modern hospital setting it is thus essential to use treatment strategies that minimize physical contact with and restraint of patients by hospital staff. Ideally, this treatment should act as quickly as possible with the fewest side effects.

DATA SOURCES

This review examines the animal and clinical studies of droperidol in the acute psychiatric setting and provides evidence that it may be the drug of choice for the agitated patient. For this purpose, we examined all pertinent English-language articles published in psychiatry-related journals via MEDLINE dating back to 1966. This search resulted in 11 articles that use *droperidol* as a text word, all of which are discussed in this review. We next examined all pertinent English-language articles published in internal medicine– or emergency medicine–related journals in which droperidol is used for psychiatric indications. This MEDLINE search dated back to 1966, and a cross-referencing of our original MEDLINE search produced 5 articles. A similar search process was used to examine articles in the anesthesia and pharmacology literature that best illustrated the side effect profile and pharmacokinetic properties of droperidol for a variety of indications. This search produced 8 articles that are referenced in this article. Finally, using our previously de-

scribed search methods, we examined the European literature for articles that were representative of the early preclinical and clinical European experience with droperidol. This search produced 4 articles that are included in this review.

STUDY FINDINGS: ANIMAL AND CLINICAL DATA

Preliminary Studies

Droperidol (initially R4749, renamed dehydrobenzperidol, previously marketed as Inapsine) was first characterized in vivo by Janssen et al. in 1963.[4] It is a butyrophenone neuroleptic and a structural analogue of haloperidol.[5] The 1963 Janssen et al.[4] report showed that in rats, droperidol has a rapidity of onset of action significantly quicker than that of both chlorpromazine and haloperidol at multiple dose ranges administered subcutaneously. They found that droperidol has a more rapid decay of action, also true in comparisons at multiple dose ranges. The drug was further described as producing catalepsy in rats, acting more strongly in this capacity than did haloperidol and chlorpromazine, predicting its efficacy for rapid tranquilization in humans. They also identified that the drug, in spite of having a potency comparable to that of haloperidol and chlorpromazine, had a toxic dose (median lethal dose) that was 10-fold greater than that of haloperidol and 5 times that of chlorpromazine when delivered in the subcutaneous route. That report on the pharmacology of droperidol in the rat model prompted human clinical research that would later suggest a unique profile of action in humans.

Case Studies and Open-Label Trials

Initial limited trials of droperidol took place in Europe, where researchers reported efficacy for patients experiencing symptoms of severe excitation, aggression, and insomnia.[6,7] Its usefulness for the longer term treatment of psychosis was demonstrated in 1970 by Cocito et al.,[7] who compared droperidol with haloperidol in 112 patients (mean dose of droperidol was 6.32 mg/day and that of haloperidol was 6.0 mg/day, all given p.o.). Antipsychotic efficacy was comparable at 30 and 60 days after initiation of therapy (all done entirely in the hospital setting).[7]

Curiously, the U.S. psychiatric literature and standard psychiatric clinical practice have favored haloperidol for use in acute agitation in spite of this earlier evidence of at least comparable clinical utility for both drugs.[8,9] The great majority of U.S. reports on droperidol are found in the anesthesiology literature, reflecting its widespread use as an augmentation for sedative, paralytic, and antiemetic treatment in surgical settings.[10,11] This may have contributed to the false notion that droperidol is in fact itself an anesthetic. Hooper[12] suggests that marketing forces have suppressed its widespread use in the United States in the psychiatric setting in favor of haloperidol, in spite of scientific evidence for its superior utility for acute psychiatric emergencies.

In 1973, Cressman et al.[13] described that in humans, as in animal models, droperidol was extremely rapidly absorbed with intramuscular injection. Blood droperidol levels were shown to rise at rates comparable to those seen with i.v. injection upon i.m. administration, suggesting that clinical response would be similar for both i.m. and i.v. routes.[13] The blood level rise of i.m. doses of droperidol were found to be close to peak levels by 10 minutes postinjection, and the drug had a half-life of 2.2 hours.[13] In contrast, haloperidol shows a peak level at around 20 minutes with a half-life of 14 to 24 hours.[14]

Noncontrolled trials of droperidol include the work of Davies and White,[15] who describe p.o. dosages of 10 to 20 mg in use in over 100 occasions in patients with schizophrenic episodes or manic behavior and for the treatment of violent behavior in patients with epilepsy, autism, or traumatic brain injury. Effects from oral doses were reported to be evident in 30 minutes and lasted approximately 4 hours.[15] Using predominantly the i.m. route, Neff et al.[16] report the use of droperidol in 32 patients with severe agitation related to acute schizophrenia, mania, and "acute brain syndromes" of various etiologies including drug-induced psychosis. Within 30 minutes, 72% had responded to the treatment as indicated by a 2-point drop on a 1-to-4 agitation scale. Over half the group had onset of action as indicated by a 1-point drop in the 1-to-4 scale within 15 minutes.[16] Granacher and Ruth[9] reported the use of droperidol in 24 agitated patients treated with a single i.m. injection of 2.5 to 12.5 mg. Twenty-two patients responded within 30 minutes.[9] Hooper[17] reported similar success in 3 cases, delivered p.o., i.v., and i.m., all revealing rapid improvement in agitation in 15 minutes.

Richards et al.[18] report their open-label, randomized comparison of droperidol with lorazepam in the emergency room for the treatment of 202 acutely agitated patients. They used droperidol doses of 2.5 or 5 mg i.v. versus lorazepam doses of 2 or 4 mg i.v. depending on patient weight. After injection, they measured sedation scores at 5-minute intervals for 15 minutes postinjection, then at the 30- and 60-minute points. They found that the group receiving droperidol (N = 102) had significantly greater sedation at the 10-, 15-, 30-, and 60-minute timepoints compared with lorazepam (N = 100). In addition, 40 patients receiving lorazepam required a second dose at 30 minutes after initial treatment, whereas only 8 patients of the droperidol group required repeated dosing. Also, the group receiving droperidol had a significantly shorter time in the emergency room (ER).

Controlled Studies

There are 2 double-blind placebo-controlled studies of droperidol for acute agitation. Van Leeuwen et al.[19] ran-

domly assigned 41 agitated psychiatric inpatients with delirium and psychoses to receive droperidol, 10 mg i.v., versus saline i.v. The need for retreatment with a standard dose of haloperidol was assessed clinically at timepoints after the initial blind injection. At 3 minutes after the initial injection, 6 of 19 who initially received droperidol required a follow-up injection of haloperidol. In the saline treatment group, 19 of 22 patients required retreatment with haloperidol at 3 minutes. At 30 minutes after initial blind injection, 4 of 19 who initially were given droperidol again required haloperidol. However, 10 of 22 of those initially receiving saline again required haloperidol at 30 minutes. Rosen et al.[20] randomly assigned 46 agitated patients in the ER setting to receive droperidol, 5 mg i.v., versus saline. Using a 5-point rating scale of severity of agitation, they determined a significant effect for the 23 patients receiving droperidol compared with placebo as early as 5 minutes and a highly significant difference at 20 minutes.

Two double-blind comparisons with haloperidol are reported in the American literature and include the work of Resnick and Burton.[11] This group randomly assigned 27 agitated psychiatric inpatients to receive 5 mg i.m. of either haloperidol or droperidol. The Brief Psychiatric Rating Scale (BPRS) was used to determine the need for a second injection. If patients scored greater than 17 on the BPRS at 30 minutes, then a second injection of haloperidol was given. At 30 minutes, 81% of the haloperidol patients required a follow-up injection of haloperidol, while 36% of the droperidol patients required a follow-up injection.[11] In the emergency department setting, Thomas et al.[21] used a 5-point agitation rating scale in the assessment of 47 patients randomly assigned to receive 5 mg of either droperidol, i.m. or i.v., or haloperidol, i.m. or i.v. Droperidol was significantly more effective at 10, 15, and 30 minutes postinjection compared with haloperidol.[21] There was a trend toward superior effect of droperidol at the 5-minute mark. No significant difference was found in efficacy between the droperidol delivered i.m. versus i.v. The patients receiving droperidol were also observed to have a lower rate of admission after treatment in the ER.

Side Effects

As with all typical neuroleptics, droperidol is known to cause extrapyramidal symptoms (EPS) and to have cardiovascular side effects such as hypotension and prolongation of QT interval with risk of torsades de pointes. The majority of these side effects are reported for surgical, obstetric, and critically ill patients as described in the anesthesia literature.[22–27] Studies of droperidol use in psychiatric populations that do not have a predominance of medical or surgical issues most clearly represent the side effect risk in psychiatric treatment settings.

The following discussion briefly discusses reports of droperidol-related side effects in studies already outlined in this review. Studies examining droperidol in the open-label format include the work of van Leeuwen et al.[19] In their comparison of droperidol with saline in 41 agitated patients, they reported no observed side effects. The use of droperidol delivered i.m. (2.5 to 12.5 mg) by Granacher and Ruth[9] in 24 agitated patients produced 1 case of dystonia and 2 cases of mild hypotension. Davies and White[15] reported no observed side effects in the use of the medication in doses of 10 to 20 mg p.o. in over 100 cases of patients having agitation associated with acute psychotic episodes, mania, traumatic brain injuries, and pervasive developmental disorders. Szuba et al.[28] conducted a retrospective review of medical records of patients receiving droperidol in emergency situations of danger to self or others and/or nonspecific agitation. They examined 385 administrations in doses of 2 to 200 mg i.m. in 271 cases and i.v. in 114 cases. They found that total dose did not influence likelihood of EPS (8% for the entire group) in a statistically significant manner and that there were no significant differences in rates of side effects between the i.m. and i.v. dosing routes.[28] One case of transient supraventricular tachycardia was observed in a 69-year-old woman treated with 50 mg i.v. In a report of 102 emergency room patients receiving 2.5 to 5 mg of droperidol i.v., no adverse effects related to vital sign changes were found.[18] One patient had a dystonic reaction that was adequately treated with diphenhydramine.

Studies comparing droperidol and haloperidol may most optimally characterize risks associated with droperidol in psychiatric patient populations. Cocito et al.[7] compared droperidol with haloperidol given orally to 45 patients needing treatment for chronic psychosis who were randomly assigned to 1 of the 2 drugs for up to 160 days. Average dose of droperidol was 6.32 mg/day and that of haloperidol was 6.0 mg/day (all given p.o.). They found that there were no large differences in side effects between the 2 drugs, although droperidol tended to cause less asthenia, tachycardia, and sialorrhea but greater akathisia and tremor, especially at initial phase of treatment.[7] Thomas et al.[21] found that for 68 patients (all presenting to the ER requiring restraint) treated with droperidol versus haloperidol, there were no significant differences between the 2 drugs in rate of blood pressure changes or reported subjective symptoms. In the same study, there were no EPS in the patients receiving droperidol (1 with haloperidol). Resnick and Burton[11] randomly assigned 16 patients to haloperidol (5 mg i.m.) and 11 to droperidol (5 mg i.m.) and found that only 1 patient in the haloperidol group had a side effect (mild dystonia). There were no significant cardiovascular changes in either group. Rosen et al.,[20] in randomly assigning 22 agitated patients to droperidol (5 mg i.v.) and 23 to saline (emergency department setting treating trauma and medical diagnoses), found no significant changes in systolic blood pressure. One patient in the droperidol group had akathisia, which was treated with diphenhydramine. These data suggest that side effects as-

sociated with typical neuroleptics occur with droperidol use at rates comparable (and perhaps less) to those reported with haloperidol, possibly owing to droperidol's much shorter half-life.

CONCLUSION

This review has summarized the early European literature and outlines the U.S. and British clinical literature that examines the use of droperidol as an antipsychotic agent and for control of agitation in the psychiatric and emergency room settings. Janssen's animal studies predicted the findings of later human clinical studies: droperidol, at least equally efficacious as haloperidol for the indication of acute agitation, has a more rapid rise in blood drug levels by i.m. injection and thus the shortest latency of onset. Additionally, it has been observed to have a side effect profile comparable to that of haloperidol, and possibly a less severe one, due to its rapid elimination from the body compared with haloperidol. The association of droperidol use with nonpsychiatric settings such as medical emergency rooms and with surgical cases may have unfortunately stigmatized its indications and side effect profiles from the point of view of psychiatrists.

In most cases of agitated patients who refuse p.o. medication, tranquilization for safety requires i.m. administration. As the primary treatment in acute psychiatric settings becomes more focused on control of dangerous behavior, there is a greater need for an optimal injectable neuroleptic that has a short latency of onset so as to prevent injury to patients and staff. In these clinical situations, droperidol should be considered a candidate as the therapeutic drug of choice, as supported by the studies outlined in this review.

Drug names: chlorpromazine (Thorazine and others), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), lorazepam (Ativan and others).

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