Losartan for treatment of psychogenic polydipsia

TO THE EDITOR: Approximately 80% of psychiatric patients who manifest psychogenic polydipsia suffer from schizophrenia.[1] This syndrome may eventually lead to complications of water intoxication such as mental status changes, seizures, coma, and even death.[2] No intervention has been definitively shown to be effective. We report a case of a patient whose excessive fluid intake was ameliorated by treatment with the angiotensin-receptor blocker (ARB) losartan.

Case Report. A 41-year-old white female with a 27-year history of schizoaffective disorder was admitted secondary to excessive fluid intake. The patient denied that any delusions or hallucinations were motivating this behavior, stating that she felt compelled to drink whenever she saw another individual with a beverage. Throughout much of her illness, she has manifested psychogenic polydipsia, which led to a generalized seizure in the past. She has no underlying medical disturbance that could account for the polydipsia. Upon admission, her medications included haloperidol, valproic acid, sertraline, quetiapine, and trihexyphenidyl. A complete blood cell count and a basic metabolic panel were within normal limits.

Following a one-week baseline period characterized by marked diurnal weight gain and high fluid intake per nursing observations, the patient was initiated on losartan 25 mg/day. This treatment ameliorated her polydipsia within a couple of days. The following week, the losartan dose was increased to 50 mg/day, resulting in further improvement per weight measurement and nursing observations. Discontinuation of losartan was attempted the next week, and the polydipsia worsened (Figure 1). The patient's blood pressure and heart rate remained stable. Her psychiatric symptoms were not exacerbated by adding losartan, which was continued at 50 mg/day.

Discussion. Central angiotensin pathways are critical in regulation of fluid intake. Dopamine may modulate the thirst-inducing effect of angiotensin II at the brain's AT_1 and AT_2 receptors.[2] This suggests that polydipsia is not solely a behavioral consequence of psychosis, but may be a unique manifestation of the dopaminergic dysfunction implicated in schizophrenic psychopathology. Indeed, our patient required readmission because of polydipsia without causal psychiatric morbidity.

To our knowledge, as of August 18, 2004, this is only the second reported use of an ARB in the treatment of psychogenic polydipsia. This case differs in a few important ways from the previous report, which describes the benefit of irbesartan in a schizophrenic patient with psychogenic polydipsia.[3] Given that both AT_1 and AT_2 receptors have been implicated in water consumption in rats fed a high amount of sodium chloride (thus mimicking a human diet), we selected losartan because it possesses the lowest AT_1 subtype specificity among the available ARBs.[4,5] Unlike the patient in the previous report, our patient was not hypertensive, yet she tolerated losartan well. Finally, we maintained the antipsychotic regimen, whereas in the prior case, a recent switch from risperidone to olanzapine likely confounded the effect of irbesartan due to the reduction in D_2 blockade and higher 5-HT_2 affinity of olanzapine. Our case further suggests the potential use of ARBs in the treatment of psychogenic polydipsia.

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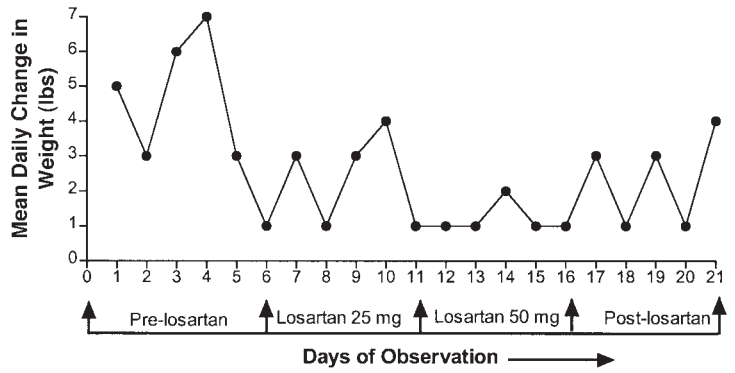

Figure 1. Improvements in daily weight fluctuations following treatment with losartan in a schizophrenic patient with psychogenic polydipsia.

REFERENCES

1. de Leon J, Verghese C, Tracy JI, Josiassen RC, Simpson GM. Polydipsia and water intoxication in psychiatric patients: a review of the epidemiological literature. Biol Psychiatry 1994;35:408-19.
2. Verghese C, de Leon J, Simpson GM. Neuroendocrine factors influencing polydipsia in psychiatric patients: an hypothesis. Neuropsychopharmacology 1993;9:157-66.

3. Kruse D, Pantelis C, Rudd R, Quek J, Herbert P, McKinley M. Treatment of psychogenic polydipsia: comparison of risperidone and olanzapine, and the effects of an adjunctive angiotensin-II receptor blocking drug (irbesartan). Aust N Z J Psychiatry 2001;35:65-8.
4. Physicians' desk reference. Montvale, NJ: Medical Economics, 2002: 2068.
5. Camara AKS, Osborn J. Central AT_1 and AT_2 receptors mediate chronic intracerebroventricular angiotensin II–induced drinking in rats fed high sodium chloride diets from weaning. Acta Physiol Scand 2001;171:195-201.

Subcutaneous furosemide

TO THE EDITOR: We have read with great interest the article by Verma et al.[1] regarding the diuretic effects of furosemide administered by the subcutaneous route to healthy volunteers. We consider this a convenient route and describe here our experience in patients who are enrolled in home hospice treatment. Eight patients (Table 1) who had in common a severe and very evolved organic pathology—heart failure (HF) without response to treatment with oral diuretics—and who presented great difficulty in obtaining and maintaining adequate intravenous access were treated.

The subcutaneous route used to administer furosemide is a well-known alternative in the treatment of dyspnea in patients with terminal illness. Thus, this administration method is proposed in the *Manual of Palliative Care* of the University of Alberta[2] and in some additional work by Goenaga et al.[3]

Our patients presented with symptoms of decompensated HF, dyspnea, peripheral edema, and inadequate response to oral furosemide (defined as failure to lose weight despite rest for 2–3 days, salt and water restriction, and orally administered furosemide 240 mg/day). After initiation of subcutaneous furosemide, all of the patients achieved a desired increase in their daily urine output. Doses given as bolus or continuous infusion (with an elastomeric device) ranged from 40 to 140 mg/day for a duration of therapy ranging from 3 days to 8 months. Among the most important adverse effects was itching that frequently occurred at the injection site. This could be due to the high pH (~9) of the furosemide solution. In all cases, butterfly needles of 25 or 23 G in diameter were used. In the 2 patients who continued treatment for prolonged periods of time, there was variable tolerance to the subcutaneous butterfly needles. In general, injection sites in the pectoral region were better tolerated than those in the extremities.

Two patients died during treatment. In one case, the patient died shortly after the onset of precordial pain; the death was likely due to ischemic cardiomyopathy. The other patient was a female with terminal cardiomyopathy who also died in her home. A third patient died secondary to progressive sarcoma after finishing the subcutaneous treatment.

Considering these cases, we conclude, as did Verma et al.,[1] that the administration of furosemide by subcutaneous route, despite injection site issues, can be a valid alternative in patients who require the use of this medicine and in whom oral, intravenous, or intramuscular administration is not possible. Additionally, as demonstrated by our cases, we consider it a simple technique that could be used in the patient's home.

Table 1. Patients Receiving Subcutaneous Furosemide[a]

Age/ Gender	Diagnosis	Creatinine (mg/dL)	Dose (mg/day)	Mode	Duration (days)
71/M	HF, ascites	1.8	40	bolus	240
76/F	HF, ascites	2.2	140	continuous	21
58/M	HF	1.1	120	bolus	21
79/M	HF	1.4	80	bolus	60
72/M	HF, ascites	2.3	40	bolus	3
68/F	HF, ascites	0.7	40	bolus	5
75/M	HF, ascites	1.8	80	continuous	8
75/M	HF, ascites	1.3	100	continuous	6

HF = heart failure.
[a]No patient responded to oral treatment.

Part of this work has been presented in abstract form at the 7º Congreso Nacional de Hospitalización a Domicilio.

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REFERENCES

1. Verma AK, da Silva JH, Kuhl DR. Diuretic effects of subcutaneous furosemide in human volunteers: a randomized pilot study. Ann Pharmacother 2004;38:544-9. DOI 10.1345/aph.1D332
2. Pereira J, Bruera E. Dyspnea. In: Palliative care handbook. Alberta Palliative Network 2000, 2001 PallCare Ednet. www.albertapalliative.net/APN/PCHB/08_Dyspnea.html (accessed 2004 Mar 22).
3. Goenaga MA, Millet M, Carrera JA, Garde C. Vía subcutánea: más fármacos. Med Pal (Madrid) 2000;7:28.

Geographic region influences pharmacy's dispensing of blood glucose test strips

TO THE EDITOR: International pharmacy practice guidelines recognize the importance of self-monitoring of blood glucose (SMBG) for patients with diabetes and promote the role of community pharmacy in supporting patients performing SMBG.[1,2] However, large differences in the rate of dispensing of test strips exist among pharmacies in the Netherlands.[3] We assessed whether variations in dispensing of blood glucose test strips can be explained by patient characteristics and geographic region.

Methods. We used data from the PHARMO-record linkage system, containing all dispensing records of 950 000 residents of 25 population-defined areas in the Netherlands.[4] The study population consisted of all incident patients with type 1 and 2 diabetes from 1991 to 2001. Complete dispensing data during that period were extracted. Using a Cox proportional hazard model, we studied the association between the community pharmacy in which the patient was registered and the time to the first test strips dispensed.

Results. Of 8233 incident patients, 19.4% were dispensed test strips at least once. Patient characteristics varied between pharmacies and, to a lesser extent, between regions. After having adjusted for these differences, the patient's community pharmacy was still independently associated with the use of test strips. Furthermore, the variation in dispensing of test strips between pharmacies in one region was considerably less than that between pharmacies in different regions (Figure 1).

Because diabetic patients visit a pharmacy on average 5–6 times per year, community pharmacists are well placed to educate and support patients performing the

complicated process of SMBG. Furthermore, there is evidence that a pharmaceutical care model for diabetes management, including training in SMBG, improves glycosylated hemoglobin and fasting plasma glucose.[5]

Our findings suggest that the chance of receiving test strips differs between community pharmacies. Moreover, the role of community pharmacy in dispensing of test strips is significantly modified by region. Several reasons for this variability exist, not all under direct control of community pharmacists. Region-specific factors, for example, distribution of test materials by mail order, reimbursement of test strip use, and availability of qualified personnel, may have a major effect on the structure and process of diabetes care activities of individual pharmacies. Other factors, however, are under control of pharmacists, for example, sufficient training or attitudes toward diabetes being a treatable disease. Since the data on pharmacy and region were coded, the relative effect of these factors will have to be studied further.

Because of the observed differences between pharmacies, not all may experience the same barriers in dispensing of test strips. This underscores that implementing practice guidelines for diabetes in community pharmacy may require different approaches. Although our observations only apply to the Dutch situation, it is not unlikely that variability in dispensing of test strips also occurs in other countries. Factors such as reimbursement, qualified personnel, and training are not unique to the Netherlands.

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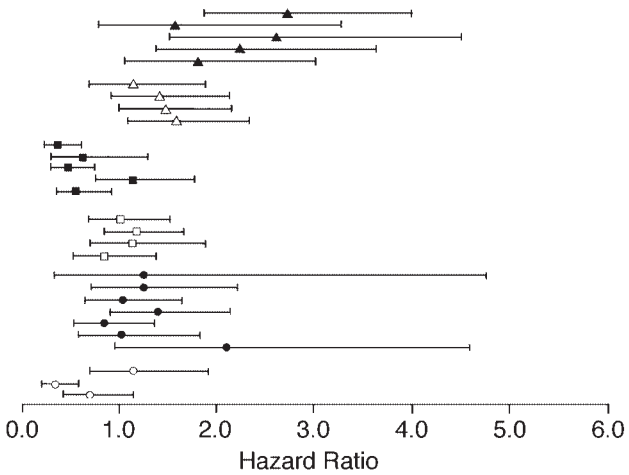

Figure 1. Association between the community pharmacy and time to first test strips dispensed adjusted for age, gender, type of treatment, year of initiation of antidiabetic drug use, and co-medication, clustered by geographic region. The symbols represent different regions. Data from regions with only one study pharmacy (11 pharmacies) have been omitted.

REFERENCES

1. ASHP therapeutic position statement on strict glycemic control in patients with diabetes. Am J Health Syst Pharm 2003;60:2357-62.
2. EuroPharmForum. Improved quality in diabetes care: the pharmacist in St Vincent team: protocol and guidelines. 2001. www.euro.who.int/document/e75680.pdf (accessed 2004 May 4).
3. Storimans MJ, Talsma H, Klungel OH, de Blaey CJ. Dispensing glucose test materials in Dutch community pharmacies. Pharm World Sci 2004; 26:52-5.
4. Herings R, de Boer A, Stricker B, Leufkens H, Porsius A. Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. Lancet 1995;345:1195-8.
5. Jaber LA, Halapy H, Fenret M, Tummalapalli S, Diwakaran H. Evaluation of a pharmaceutical care model on diabetes management. Ann Pharmacother 1996;30:238-43.

Comment: therapy switching in patients receiving long-acting opioids

TO THE EDITOR: Given the paucity of pharmacoeconomic analyses of chronic pain management, the article by Berger et al.[1] concerning switching of opioid therapy was of considerable interest. Information from a large database of pharmacy claims suggested that noncancer patients receiving controlled-release (CR) oxycodone switched to an alternative analgesic less frequently than patients receiving CR morphine, with decreased overall healthcare costs. From this information, the authors surmised that healthcare costs could be reduced by minimizing drug therapy switches, with the implication that placing patients on oxycodone may help to achieve this goal.

The method employed by Berger et al. relies on adjusting survival curves with covariates. However, if some of the main effect correlates with the covariates, any adjustment violates the assumption of parallel regression, invalidating the results. This is important because the analysis of Berger et al. failed to examine several potential confounding variables, including the severity of disease (either the primary disease causing pain or the severity of comorbid conditions), differences in socioeconomic status, and quality of treatments.

Cost differences may arise from patients being nested within severity categories. Patients with more severe disease may have been prescribed one treatment (eg, morphine) over others and would be expected to have higher healthcare costs overall. Stratifying patients by cost categories and using a propensity scoring method would likely eliminate a significant amount of the differences between the therapy groups.

It is not clear whether there were disparities in healthcare plans (eg, percentage of patients in health maintenance organizations vs preferred provider plans) that might reflect differences in prescribing practices and socioeconomic status, an important predictor of morbidity.[2]

Inappropriate prescribing and ineffective pain management are common, and patients prescribed one drug may be receiving better pain management than patients receiving the comparator, particularly if there are socioeconomic differences between groups.[3] The same argument applies to comorbid conditions, such as depression, in which treatment efficacy could significantly affect patient pain and opioid switching.

The differences in healthcare charges observed in Berger et al.'s cohort of patients appear large: for patients who switched opioids, costs were $9666 and $18 641 higher for patients without cancer and with cancer, respectively. In cost-utility models of long-acting opioids, there is only an incremental increase in drug cost per quality-adjusted life-year.[4] The differences in costs observed by Berger et al. likely reflect underlying differences in factors such as preexisting conditions, comorbidities, disease severity, and effectiveness of treatment rather than costs associated with drug switching.

Despite unanswered questions, this analysis is a positive step, and additional study is warranted to assess the complex relationship between chronic long-acting opioid use and total healthcare costs. Our current un-

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published data intersect with that of Berger et al. in identifying certain subsets of patients (younger, healthier) who are more likely to receive CR oxycodone therapy as opposed to CR morphine or transdermal fentanyl. The application of more powerful statistical methods (propensity scoring and multivariate analyses) may improve the ability to detect variations uniquely associated with the effect of long-acting opioids, prescribing patterns, and related healthcare costs.

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REFERENCES

1. Berger A, Hoffman DL, Goodman S, Delea TE, Seifeldin R, Oster G. Therapy switching in patients receiving long-acting opioids. Ann Pharmacother 2004;38:389-95. DOI 10.1345/aph.1D019
2. Ferrer RL, Palmer R. Variations in health status within and between socioeconomic strata. J Epidemiol Commun Health 2004;58:381-7.
3. Goulding MR. Inappropriate medication prescribing for elderly ambulatory care patients. Arch Intern Med 2004;164:305-12.
4. Neighbors DM, Bell TJ, Wilson J, Dodd SL. Economic evaluation of the fentanyl transdermal system for the treatment of chronic moderate to severe pain. J Pain Symptom Manage 2001;21:129-43.

AUTHORS' REPLY: We thank Dr. White for his interest in our study.[1] He seems to identify 2 basic problems: a putative failure to control adequately for confounding and our analytic approach. We agree that socioeconomic status, disease severity, and quality of treatment all may relate to therapy switching and healthcare charges. Unfortunately, computerized healthcare databases typically do not contain information concerning these factors. Presumably, variation in socioeconomic status may have been limited because all patients in our study were insured by private US healthcare plans (eg, pts. with Medicaid coverage were excluded). Moreover, we believe that healthcare charges (which were used in our analyses) to some extent correlate with disease severity (ie, pts. who are more severely ill are more likely to incur higher healthcare charges). We also explicitly noted that patients beginning therapy with CR morphine or transdermal fentanyl appeared "…sicker and/or in greater pain and therefore may have been more predisposed to switch therapy. The degree to which residual confounding affects our results is therefore unknown, and caution is accordingly warranted in interpretation of our findings."

With respect to our analytic approach, Dr. White is correct that we assumed homogeneity of effect across all measured covariates. Due to the potential for small sample sizes, we did not examine whether this assumption was satisfied for all measured covariates. However, the direction of effect was similar among patients with and without cancer (ie, our assumption appeared correct for this important covariate). We believe our use of multivariate ANCOVA and Cox proportional-hazards models yielded estimates that controlled for potential confounders identified in our database. Use of propensity matching would not be expected to provide additional benefit because it cannot control for bias due to unmeasured variables (ie, were the same variables to be used to run propensity-matched analyses, similar findings would be expected).[2]

Finally, Dr. White notes, "In cost-utility models of long-acting opioids, there is only an incremental increase in drug cost per quality-adjusted life-year." Not only does the cited study have numerous methodologic flaws,[3] but it focuses attention on the estimated cost of pain control with long-acting opioids,[4] while we analyzed total healthcare charges for patients who did and did not switch opioid therapy. We note that, in our analysis, the cost of pain-related medications comprised only 6% of total healthcare charges over 6 months among patients without cancer who did not switch therapy and 5% of total charges among their counterparts who switched therapy (corresponding values among patients with cancer were 2% and 2%, respectively). We further note that we never attributed the differences in charges between those who did and did not switch to the act of switching itself, but stated "…it does not necessarily follow that therapy switching is the cause of these higher charges."

We are pleased that Dr. White's unpublished data confirm our finding that patients who begin therapy with CR oxycodone appear to differ in important respects from those who initiate therapy with CR morphine or transdermal fentanyl. We look forward to the opportunity to examine his analyses on long-acting opioids, prescribing patterns, and healthcare costs once they become available.

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REFERENCES

1. Berger A, Hoffman DL, Goodman S, Delea TE, Seifeldin R, Oster G. Therapy switching in patients receiving long-acting opioids. Ann Pharmacother 2004;38:389-95. DOI 10.1345/aph.1D109
2. Braitman LE, Rosenbaum PR. Rare outcomes, common treatment: analytic strategies using propensity scores. Ann Intern Med 2002;137:693-5.
3. Oster G. Re: economic evaluation of fentanyl. J Pain Symptom Manage 2001;22:540-1.
4. Neighbors DM, Bell TJ, Wilson J, Dodd SL. Economic evaluation of the fentanyl transdermal system for the treatment of chronic moderate to severe pain. J Pain Symptom Manage 2001;21:129-43.

Correction: September 2004 Supplement—Treatment of respiratory infections and innovative solutions to the evolving problem of resistance

The articles appearing in the September 2004 supplement (2004;38:S7-23) were not peer reviewed.

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Letters are subject to review prior to acceptance. They should address areas related to pharmacy practice, research, or education, or articles recently published. Corrections of previously published material also are accepted. Letters are limited to no more than five authors. In cases where adverse drug effects are described, the Naranjo ADR probability scale should be used to determine the likelihood that the adverse effect was drug-related (Clin Pharmacol Ther 1981;30:239-45). Text: limit 500 words. References: limit 5. Art: limit 1 table or figure.