Mechanical Misadministration of an Oral Hypoglycemic Agent

Hypoglycemia is a serious and relatively common occurrence among hospital patients (1). In addition to factors such as renal insufficiency and hepatic disease, medication misadministration may also account for hypoglycemic episodes. We report two cases in which glyburide (Micronase, Upjohn Pharmaceuticals) was inadvertently administered to hospitalized patients because of its similar appearance to oxybutynin hydrochloride (Ditropan, Marion). Furthermore, this medication error occurred in spite of a mechanized pill sorting device utilized to improve and preserve the security of in-hospital prescribed medications.

Patient 1

A 74-year-old white male with a history of Parkinson's disease and a right cerebral vascular accident was found unconscious and admitted to the Veterans Affairs Medical Center in Providence, RI, with a serum glucose level of 27 mg/dl. At the time of transfer, listed medications included fludrocortisone for orthostatic hypotension, oxybutynin hydrochloride for urinary incontinence, L-Dopa, cimeditine, and acetaminophen. A review of the side-effect profiles of his listed medications did not elucidate a clear etiology for his hypoglycemia, and a thorough investigation of written orders and medication package labels did not reveal any medications other than those listed above. However, careful inspection of the contents of the patient's unit-dose medication packages revealed that the packages labeled oxybutynin hydrochloride 5 mg actually contained 5 mg Micronase-brand glyburide tablets. The hospital pharmacy was notified, and the patient's serum glucose levels stabilized over the next 2 days.

Patient 2

A 76-year-old white male with metastatic lung cancer and depression was admitted to the Veterans Affairs Medical Center in Providence, RI. Fasting blood glucose levels between 60 and 70 mg/dl were noted, after previous values had been consistently between 110 and 140 mg/dl. Because the patient was noted to be taking oxybutynin hydrochloride for urinary incontinence, the possibility of the substitution of Micronase-brand glyburide in place of oxybutynin hydrochloride was considered. Inspection of his medications proved this to be the case, and the patient's blood glucose levels returned to their baseline after the sulfonylurea was discontinued.

Discusssion

In a survey of 94 hospitalized patients with documented blood glucose levels ≤47 mg/dl, Fischer et al. (1) noted an overall mortality rate of 27%. Of these patients, only nine had been admitted for diabetes control. Factors such as renal insufficiency, liver disease, insulinoma, treatment of hyperkalemia, and medications have all been noted to play some role in the etiology of hypoglycemic episodes. In fact, medications are the most common cause of hypoglycemia both in and out of the hospital (2). β-adrenergic blocking agents have been implicated, as have medications as diverse as haloperidol and propoxyphene in the presence of inanition, metastatic cancer, and renal insufficiency (2). However, the majority of noninsulin drug-induced hypoglycemic incidents are secondary to oral hypoglycemic agents. Seltzer's review of 1,418 cases of documented hypoglycemia from 1940 to 1976 demonstrated that sulfonylureas were responsible for 70% of the hypoglycemic episodes (3). Factors leading to sulfonylurea-induced hypoglycemia include the insidious onset of drug activity, drug-drug interactions, impaired drug excretion and metabolism, and pharmacy error. Particularly alarming is the serious morbidity and mortality associated with sulfonylurea use in those without diabetes. Seltzer's review demonstrated 56 cases of coma induced by sulfonylurea ingestion in nondiabetic patients (3), and Scala-Barnett et al. (4) describe one case in which a dispensing error led to a fatal chlorpromamide ingestion in a nondiabetic patient.

We present two cases of nondiabetic patients who were accidentally given oral hypoglycemic agents. One was seriously affected, with two episodes of coma. Although there are numerous documentations of "sound-alike" medication errors, such as Dymelor for Diamox (5,6) or chlorpromazine for chlorpromamide (7), the cases described here appear to be the result of the similar appearance of 5 mg Ditropan and 5 mg Micronase tablets. Klonff et al. (8) describe one case in which a patient's home health attendant inadvertently switched Ditropan with Micronase because of their similar appearances, resulting in severe hypoglycemia (8). What makes our cases noteworthy and especially alarming is the in-hospital mechanism by which the medication errors occurred.

The Veterans Affairs Medical Center in Providence, RI, uses an automatic pill sorting device in the inpatient pharmacy. This machine sorts individual tablets from bulk containers into sealed unit-dose labeled envelopes for distribution to the hospital floors. Thus, if tablets are loaded incorrectly, the medications will be falsely identified by their labeled packages. Both Micronase and Ditropan are small scored blue-colored tablets, and it is likely that their similarities in appearance prevented prompt discovery of their exchange.

Conclusion

We outline two cases of mechanical misadministration of an oral hypoglycemic agent. In short, a new mechanism for iatrogenic disease is described. Even in situations in which medication packaging is mechanized and therefore assumed secure, careful inspection of all medications intended for patients with otherwise unexplained episodes of hypoglycemia is critical.

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Increased Prevalence of NIDDM in Anterior Uveitis

Anterior uveitis refers to inflammation involving the anterior portions of the eye, namely, the iris and ciliary body. The exact etiology of this process is often not clear, with ~25–50% of all uveitis patients considered as idiopathic (1–3). However, it is well recognized that numerous infectious and autoimmune endogen diseases may be causally implicated. The latter category includes specific ocular syndromes and systemic diseases, such as sarcoidosis, rheumatic diseases, Behçet's disease, and even diabetes (3). The association of diabetes and anterior uveitis was first described more than 100 years ago (4). More recently, Rothova et al. (5), in a retrospective analysis of 340 cases of anterior uveitis, found a definitive association with IDDM. Moreover, up to 75% of 16 patients with idiopathic uveitis and IDDM suffered from severe diabetic complications, including angiopathy, nephropathy, and neuropathy (5). In the same way, studies performed with a series of diabetic patients confirmed this association and also found a high frequency of systemic complications in diabetic patients with anterior uveitis (6,7). Guy et al. (7) observed iritis in 30% of 47 patients with IDDM and severe autonomic neuropathy, compared with 0.7% of 143 control IDDM patients without neuropathy. In a prospective study on patients with clinical diagnosis of unknown etiology uveitis, we have found an unexpected high frequency of NIDDM associated with idiopathic anterior uveitis. The study included 111 consecutive patients who were referred to the uveitis unit of the "Virgen de las Nieves" University Hospital of Granada, Spain, with the diagnosis of unknown etiology uveitis. The first aim of the study was to establish the etiology of uveitis in patients without any potential previously diagnosed etiological disease. Patients with ocular disease caused by late microvascular complications of diabetes were therefore excluded. There were 51 males (46%) and 60 females (54%) with a mean age of 42.7 years, range 4–83. Location of uveitis was as follows: 78 anterior (70.3%), 7 intermediate (6.3%), 19 posterior (17.1%), and 7 panuveitis (6.3%). The study protocol included clinical history, physical examination, hematological and serum biochemical analysis, erythrocyte sedimentation rate (ESR), rheumatoid factor, antistreptolysin-O (ASLO), C-reactive protein, antinuclear antibody (ANA), serologic study for syphilis, toxoplasmosis and virus, mantoux, chest and sacroiliac X-ray and HLA B27 typing in case of anterior uveitis. Diabetes was defined according to criteria of the World Health Organization (8). After evaluation, 54 patients were declared to have an idiopathic uveitis (48.6%), and a specific diagnosis was confirmed in 57 patients. Of these, 11 (9.9%) had a specific ocular condition, and 41 (36.9%) had an underlying systemic disorder. The most frequently observed systemic diseases were HLA-B27–associated seronegative spondylarthropathies (12.6%) and Behçet's disease (4.5%). We used the χ^2 test and Fisher's exact test for statistical analysis. A P value of <0.05 was considered to indicate statistical significance. Diabetes was observed in five nonobese patients (two men and three women, mean age 64.8 years with an age range of 55–74 years), all of them with idiopathic and anterior uveitis. Only one patient had been previously diagnosed with diabetes about 2 years ago, which was managed with diet. Two patients had bilateral ocular involvement, two developed chronic or recurrent inflammation, and none had posterior synechiae, glaucoma, retinopathy, or iris neovascularization. The frequency of diabetes in patients idiopathic anterior uveitis was 14.3% (5 of 35 patients), compared with no case in the group of 43 anterior uveitis patients with an established diagnosis ($P = 0.01$). This percentage is significantly higher than the prevalence of diabetes in a normal Spanish population (5.6%) ($P < 0.001$) (9).

In conclusion, we found a definitive association between NIDDM and idiopathic anterior uveitis. Although such association has been previously observed in one third of 30 patients with anterior uveitis and diabetes, statistical significance was not achieved (5,6). The pathogenic significance of this association is unknown. Previous studies have postulated that microangiopathy produced by diabetes could induce ischemic processes in the anterior uvea with subsequent tissue reaction and clinical features of anterior uveitis (5,6), but such a mechanism is unlikely in newly diagnosed patients with NIDDM who have no clinical evidence of microvascular complications. However, iris fluorescein angiography could be useful to clarify whether uveitis is an ischemic phenomenon in these patients. On the other hand, the absence of retinopathy, recurrent episodes in some patients, and a usually good response to corticosteroid therapy suggest an inflammatory process (5). This is quite possible in those immunologically mediated diseases such as IDDM, but is difficult to understand in the case of NIDDM. Castagna et al. (6), in a recent study of peripheral lymphocyte subsets in patients with anterior uveitis and diabetes, found normal values in patients with NIDDM, while a significant increase in the $CD8^+$ subset together with a $CD4^+/CD8^+$ ratio decreased in all IDDM patients. Lastly, a careful monitoring of the ocular inflammatory processes presenting in diabetic patients, and probably a prospective more extensive study could help to elucidate whether anterior uveitis in NIDDM patients is a causal or a true relationship.

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