



Reversible Worsening of Psychosis Due to Benzydamine in a Schizoaffective Young Girl Who is Already under Treatment with Antipsychotics

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ÖZET:

Antipsikotiklerle tedavi altında olan şizoaffektif bir genç kızda benzydamin kullanımına bağlı olarak gelişen reversibl psikoz kötüleşmesi

Ülkemizde Tantum, Tanflex, Benzidan gibi isimlerle satılan benzydamid hidroklorid, antienflamatuar ve analjezik olarak sıklıkla kullanılan bir ilaçtır. 500 ilâ 3000 mg gibi oral dozlarda "deliran" (kafa bulucu) etkisi görülür; yaratıcılığı artırıcı hallüsinozise (ego-distonik hallüsinasyonlara) ve öforiye yol açtığı için, Polonya ve Brezilya'da sıklıkla kullanılmaktadır. Yüksek dozlarda panoya, ağzı kuruluğu ve konvülsiyonlar görülebilir ve 2000–3000 mg dozlarında merkezi sinir sistemini uyarıcı etkisi belirginleşir. Bu "trippler" bilerek veya kazaan alınan yüksek dozlardan sonra ortaya çıkıp, ilaç kesilince 2 ilâ 3 günde kendiliğinden düzelir. Günde 40 mg sitalopram, 80 mg ziprasidon ve hafif akatizi için verilen 6 mg biperiden ile üç senedir hemen tamamen düzelmiş durumdaki bir genç kız hastamda basit bir ortopedik sorun için gittiği ortopedistin yazdığı Tantum Draje (50 mg) günde üç kez kullandıktan hemen sonra hallüsinozis, disfori ve paranoid ideasyon gelişip, ilâci 5. gün kestikten sonra 5 günde tekrar normal hâline döndü. Nörolojik muayenesinde, ayrıntılı laboratuvar tetkiklerinde hiçbir anormallik bulunmadı.

Araştırılabildiğim kadariyle, zâten psikotik olup da ilaç tedavisi altında bulunan bir hastada, klinik dozlarda dahi hallüsinozis gelişen ilk vak'a takdimi budur. Gerçekte ise bu sorunun daha sık olduğunu ve bu ilacı yazmadan önce, hangi daldan olursa olsun, hekimlerin geçmiş veya hâlen mevcut bir psikiyatrik sorunu, bilhassa psikozu sorgulamaları gerektiğini düşünüyorum.

Anahtar sözcükler: Benzydamine, hallüsinozis, ilaçla indüklenen psikoz, madde suiistimali

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ABSTRACT:

Reversible worsening of psychosis due to benzydamine in a schizoaffective young girl who is already under treatment with antipsychotics

Benzydamine, available as the hydrochloride form, is an anti-inflammatory drug providing both rapid and extended pain relief in many painful inflammatory conditions. In oral dosages of 500 mg to 3000 mg it is a "deliriant" and CNS stimulant, popular in Poland and Brazil. In Brazil it is so popular that many people use it for recreational purposes. A person in a "benzydamine trip" may experience a feeling of well-being, euphoria and in higher doses hallucinations, paranoia, dry mouth and convulsions may also be experienced. In dosages of 750 mg to 2000-3000 mg benzydamine is a hallucinogen and CNS stimulant. These "triple" effects may be observed in poisoning or accidental or "on purpose" overdose cases also, hallucinosis (i.e. ego-dystonic hallucinations) is typical in such cases and generally remits spontaneously in 2 to 3 days after cessation of the drug even in children.

I report a 22 years-old schizoaffective patient under almost complete remission with citalopram 40 mg, ziprasidone 80 mg and biperiden 2 mg tid for mild akathisia. She was almost symptom-free for three years. She had a leg injury and an orthopedist prescribed Tantum pills 50 mg tid after meals. On the second day she was hallucinated with complete insight (i.e., hallucinosis), dysphoric and slightly paranoid; like her initial complaints. She used the drug for totally 5 days. When I examined her on the 6th day, she was vigilant; her orientation and judgment were intact, excluding the diagnosis of delirium. There was nothing abnormal in her neurological examination and laboratory testing including CBC, liver, kidney and thyroid functions. We quitted benzydamine and did nothing else except waiting for the course. It took her 5 days to become symptom-free again. She had no recurrent complaint or persisting hallucinosis. Although there is no previously published information about this hallucinogenic and deteriorating effect of benzydamine in a psychotic young person, physicians including orthopedist, dermatologists etc planning to prescribe benzydamine to their patients should concern and must take at least a brief anamnesis for previous or ongoing psychotic disorder.

Key words: Benzydamine, hallucinosis, drug induced psychosis, substance abuse

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INTRODUCTION

Benzydamine [3-(1-benzyl-1H-indazol-3-yloxy)-N,N-dimethylpropan-1-amine] (marketed as Tantum, Tanflex, and Benzidan in Turkey), available as the hydrochloride

form, is a anti-inflammatory drug with local anesthetic and analgesic properties providing both rapid and extended pain relief as well as a significant anti-inflammatory treatment for the painful inflammatory conditions of the mouth and throat. It selectively binds to

inflamed tissues as a weak prostaglandin synthetase inhibitor is thought to be virtually free of any adverse systemic effects. It may be used alone or as an adjunct to other therapy giving the possibility of increased therapeutic effect with little risk of interaction (1). It is well absorbed after oral intake and effective blood level is reached in 1 hour, lasting up to 4-6 hours. It is relatively less-protein bound than other non-steroid anti-inflammatory agents (15-20%), which increases the drug's bioavailability. It is more concentrated in inflamed tissues than normal tissues; elimination half-life is about 24 hours, excreted by liver and kidneys partially unchanged, and partially as metabolized.

It is also a systemic anti-inflammatory drug which is widely available and used topically for the treatment of the mouth, as a gel for application to inflamed joints and vaginal problems, and as a pill for systemic use. Its physicochemical properties and pharmacological activities differ markedly from those of the aspirin-line non-steroidal anti-inflammatory drugs; i.e. it is a weak base unlike the aspirin-like drugs which are acids or metabolized to acids, and a major contrast with the aspirin-like drugs is that benzydamine is a weak inhibitor of the synthesis of prostaglandins but it has several properties which may contribute to its anti-inflammatory activity. These properties include inhibition of the synthesis of the inflammatory cytokine, tumor necrosis factor-alpha (EC₅₀, 25 micromoles/L). Inhibition of the oxidative burst of neutrophils occurs under some conditions at concentrations of 30 to 100 micromoles/L, all are concentrations which may be produced within oral tissues after local application. A further activity of benzydamine is a general activity known as membrane stabilization which is demonstrated by several actions including inhibition of granule release from neutrophils at concentrations ranging from 3 to 30 micromoles/L and stabilization of lysosomes. Lack of knowledge of the tissue concentrations of benzydamine limit the chance of making a reasonable correlation between its in vitro and in vivo pharmacological activities. The concentration of benzydamine in the mouthwash is 4 micromoles/L but the concentrations in oral tissues have not been studied adequately. Limited data in the rat indicates that concentrations of benzydamine in oral tissues are approximately 100 micromol/L (2). Unlike other NSAIDs, it does not inhibit cyclooxygenase or

lipooxygenase, and is not ulcerogenic.

It is available in a mouth wash named Tantum Verde across Europe. In the UK it is sold by 3M under the trade name Difflam, as Difflam Spray, Difflam Oral Rinse and Difflam Cream. Its high cost (about £7 a bottle) makes it less attractive than the cheaper method of gargling aspirin. In Australia it is available from 3M as Difflam-C Alcohol & Color Free Solution, Difflam 3% Gel, Difflam Extra Strength Gel 5%, Difflam-C Solution, Difflam Solution (including Difflam Throat Spray), Difflam Cream and Difflam Lozenges. It is sold in Eastern Europe without prescription as Tantum Rosa - a vaginal antiseptic and anti-inflammatory, containing 0.14 g of benzydamine hydrochloride to be reconstituted with clean water to a 0.1% (1 mg/mL) solution for vaginal enema/instillation. In Brazil it is sold by prescription under the name "Benflogin", with each box containing 20 pills (50mg each). In Pakistan it is sold by prescription under the name Tantum Capsule (50mg). It is available in a cream and gel named Tantum Fort across Egypt by EIPICo. It is available with prescription as a mouthwash named Novo-Benzydamine (Novopharm) in Canada. In Turkey, like many other medications, it is cheap and sold over the counter in all pharmacies as Tantum, Tanflex, and Benzidan; which make it a very easily reachable, consumable, and abusable drug!

Main indications are in odontostomatology, gingivitis, stomatitis, glossitis, aphthous ulcers, dental surgery and oral ulceration due to radiation therapy; in otorhinolaryngology pharyngitis, tonsillitis, post-tonsillectomy, and radiation or intubation mucositis, in general inflammatory diseases, bruising, tendonitis, bursitis, burns etc. Oral dose is 0.7-1 mg/kg (50 mg) tid after meals; if required, 1 additional pill may be added; maximum daily dose is four pills a day, with mean therapy duration of 5 to 15 days (3).

Benzydamine is well tolerated. Occasionally oral tissue numbness or stinging sensations may occur. Benzydamine may be abused recreationally. In oral dosages of 500 mg to 3000 mg it is a "deliriant" and CNS stimulant, popular in Poland and Brazil. In Brazil it is so popular that many people use it for recreational purposes. A person in a "benzydamine trip" may experience a feeling of well-being, euphoria and in higher doses will hallucinate, paranoia, dry mouth and convulsions may also be experienced. The trip can last up to 8 hours, after that the user becomes tired and

quiet, but sleeping is almost impossible. In dosages of 750 mg to 2000-3000 mg benzydamine is a hallucinogen and CNS stimulant (4). These “triply” effects may be observed in poisoning or accidental or “ingested on purpose” cases also (5), hallucinosis (i.e. ego-dystonic hallucinations) is typical in such cases and generally remits spontaneously in 2 to 3 days after cessation of the drug even in 6-year-old children (6).

These psycho[so]mimetic and hallucinogen properties are very important. Hallucinogens which are also named as psychomimetics or psychedelics are substances whose consumption causes hallucinations, delusions and illusions. They can be synthetic or may be found naturally. Psychedelic is an English term coined from the Greek words for “soul” (psyche), and “manifest” (delos). A psychedelic experience is characterized by the perception of aspects of one's mind previously unknown, or by the creative exuberance of the mind liberated from its ostensibly ordinary fetters. Psychedelic states are an array of experiences elicited by sensory deprivation as well as by psychedelic substances. Such experiences include hallucinations, changes of perception, synesthesia, altered states of awareness, mystical states, and occasionally states resembling psychosis. Psychedelics are used for “therapy” in the broadest possible sense of the term is likely as old as humanity's ancient knowledge of hallucinogenic plants itself. Though usually viewed as predominantly spiritual in nature, elements of psychotherapeutic practice can be recognized in the entheogenic or shamanic rituals of many cultures (7). The use of psychedelic agents in Western therapy began in the 1950s, after the widespread distribution of LSD to researchers by its manufacturer, Sandoz Laboratories. Research into experimental, chemotherapeutic and psychotherapeutic uses of psychedelic drugs was conducted in several countries over the next 10-15 years. In addition to the release of dozens of books and creation of six international conferences, more than 1000 peer-reviewed clinical papers detailing the use of psychedelic compounds (administered to approximately 40,000 patients) were published by the mid 1960's. Proponents believed that psychedelic drugs facilitated psychoanalytic processes, and that they were particularly useful for patients with problems that were otherwise difficult to treat, including alcoholics, although the trials did not meet the methodological standards required today (8). Studies

by Humphrey Osmond, Betty Eisner, and others examined the possibility that psychedelic therapy could treat alcoholism (or, less commonly, other addictions). A review of the usefulness of psychedelic therapy in treating alcoholism concluded that the possibility was neither proven nor disproven (9). Current legal research into possible therapeutic value of psychedelics has been ongoing for several years. The only published pilot study so far is one that showed that Psilocybin could be safely given to those with Obsessive Compulsive Disorder and showed trends for improvement of symptoms but the study did not clearly establish whether or not the patients were helped by the treatment (10).

Although some novel researches are planned about using hallucinogens/psychedelics in variety of medical diseases, they do not have any evidence-based value for anyone since the time this article is written. But the contrary is a fact!

Social and recreational use of drugs follows waves of popularity, and there are also regional phenomena and preferences particular to certain subpopulations. Lesser-known drugs may be used in certain groups. For instance, younger gay men in urban areas who use “circuit” (a series of weekend-long parties that focus on dancing and sex) may be users of “party” drugs that include methamphetamine; MDMA (3,4-methylenedioxy-methamphetamine), or “Ecstasy”; GHB (γ -hydroxybutyrate); ketamine; nitrate inhalants (poppers); and LSD (lysergic acid diethylamide) and other hallucinogens (11).

The hallucinogenic effects of these drugs are related to decreased serotonin turnover in brain. 5HT₂ receptor antagonists can inhibit the hallucinogenic effect (12). If her relation with me was not strong enough, she might even visit an emergency service; which is not uncommon for such cases (13).

Interestingly, I could not find any mention about benzydamine as a hallucinogen or even as a psychotropic medication (14). Hallucinogens/psychedelic agents or drugs are hazardous in all means; e.g. socially, morally, medically, economically, and psychiatrically. They may cause hallucinogen persisting perception disorder (HPPD) which is a disorder characterized by a continual presence of visual disturbances that are reminiscent of those generated by the ingestion of hallucinogenic substances. Previous use of hallucinogens is needed, though not

sufficient, for diagnosing someone with the disorder. For an individual to be diagnosed with HPPD, the symptoms cannot be due to another medical condition. HPPD is distinct from flashbacks by reason of its relative permanence; while flashbacks are transient, HPPD is persistent. It is not known how frequently people develop HPPD. In their review article, John Halpern and Harrison Pope write that “the data do not permit us to estimate, even crudely, the prevalence of ‘strict’ HPPD” (15). I diagnosed just one case in my 25 years’ professional life.

CASE

AI, now 22 years old, is under my treatment since she was 17 with a definite diagnosis of schizoaffective disorder (both for DSM-IV-TR, and for ICD 10) with good prognostic features and a favorable response to therapy. Her routine EEG and sleep EEG, laboratory testing including CBC, vitamin B12 and folate levels, thyroid, liver and kidney functions.

Initially, she had mood swings and auditory hallucinations which were worsened with fluoxetine, including insomnia, dysphoric hypomania, feeling some supernatural “things” wondering around and mild paranoid ideation; she always had some intellectual insight. I prescribed lamotrigine 25mg with quetiapine 200 mg at night time. Her psychotic symptoms and dysphoric mood remitted in three weeks time. Her lamotrigine was increased to 300 mgs per day by time but because of the rapid weight gain and her discomfort about her appearance and unexplained mild increase in her parathormone with significant osteoporosis, and some non-significant skin lesions, I reduced and quitted her lamotrigine, replacing it with citalopram 40 mg. My second novel antipsychotic choice was aripiprazole with success in psychiatric complaints but causing serious akathisia which did not respond neither to propranolol, nor to biperiden. When I switched the dopamine antagonist to ziprasidone 80 mg at dinner it was efficacious (her all electrocardiograms were completely normal, with normal QTC); but though it was reduced, I had to go on giving her biperiden 2 mgs tid for milder akathisia. After these fine adjustments, she was stabilized with all the drugs (16). She stayed almost symptom-free for three years, visiting me regularly for psychotherapy about her adolescence problems. There were no problems in her

laboratory measures and her osteoporosis remitted with calcium supplement.

When I was in Europe for the ECNP Congress, she had a leg injury and the orthopedist she visited prescribed Tantum pills 50 mg tid after meals. Because of not attributing importance for the condition, she began to take it without asking me. On the second day she was hallucinated with complete insight (i.e., hallucinosis), dysphoric and slightly paranoid; like her initial complaints five years ago. She used the drug for totally 5 days, her pain was gone but her psychiatric symptoms were deteriorating. When I examined her on the 6th day, she was vigilant; her orientation and judgment were intact, excluding the diagnosis of delirium. There was nothing abnormal in her neurological examination and laboratory testing including CBC, liver, kidney and thyroid functions. We quitted benzydamine and did nothing else except waiting for the course. It took her 5 days to become symptom-free again. She had no recurrent complaint or persisting hallucinosis.

DISCUSSION

Available literature is surprisingly poor and highly concentrated about childhood, even infancy, so about pedopsychiatry as stated by Eggers (17): “By introducing the definition ‘hallucinosis’ (Wernicke) it has become possible to confine the psychoses of organic origin more closely. Therefore, this term should also be used in pediatry and pedopsychiatry in order to designate cases with corresponding clinical aspects. Thus, accordance to the phenomenological characteristics of such syndromes as described in this paper, it is justified to emphasize that the acute hallucinosis in children is a special type of disease as compared to other psychoses caused by exogenic influences in this age group. The 10 case reports deal with visual hallucinosis which turned out to be characteristically different compared to those in adults. Hallucinating children at the age of 3 to 9 years predominantly visualized animals and legendary beings. Contrary to findings in adults, scenic and systematized visions were scarcely noticed, which psychodevelopmentally may be attributed to the fact that creative power in children is still little pronounced. Etiologically intoxications and infectious diseases were the cause for the visual hallucinations of the 10 children described. In the development of visual

hallucinations somatic and psychic factors are significant. They have been discussed on the basis of today's knowledge. As today, however, there exists no satisfactory theory concerning the conditions favoring the development of hallucinations. To explain the somatogenesis of visual hallucinations three theories have been outlined, based on the present neurophysiologic findings. It has been worked out that especially in children emotion plays an essential role in the origin of hallucinations. In infancy and early school age, while rational control of reality is still suppressed to a great extent, domination of emotional life goes along with lack of differentiation. At the same time the difference between imagination and perception is still little precise; therefore, phenomena, impressing as hallucinations in the adult, occur with greater facility in children.

On the other hand, as Anand et al. stated (4), it is a highly abused drug in some countries like Poland and Brazil with the market name of Benflogin. I am not aware of any survey or research about the misuse or abuse of benzydamine in different age groups.

In our case, hallucinosis appeared in clinically normal doses and subsided in 5 days. The reason and mechanism does not seem like a simple pharmacokinetic or pharmacodynamic interaction. Rather, it is the exacerbation of the psychosis under control (18).

As stated by Altınbaş et al. (19) psychiatric symptoms aggravated by psychoactive drug abuse and primary psychosis cause the diagnostic uncertainty like the paradox about chicken or egg. There is strong evidence about alcohol, cannabis, amphetamine, cocaine and inhalant induced psychosis in literature. Although classical antipsychotics are effective in the treatment of substance induced psychosis; second generation antipsychotics have advantages due to positive effects on

substance seeking behavior and lower extrapyramidal side effects. But, in this case, there was no substance abuse except smoking cigarettes. Personality disorders are one of the most common comorbid psychiatric disorders found in adults with substance use disorders; comorbidity of any personality disorder is associated with increased substance use related problems and poorer long term outcomes (20). Our case does not have any personality disorder as a comorbid or aggravating phenomenon.

CONCLUSION

As far as I know, this is the first case reported about usage of benzydamine in a young psychotic patient in clinically normal doses resulting with hallucinosis, despite her current usage of antipsychotic medication and a mood stabilizer (carbamazepine).

Although this is just one case, which unfortunately could be the last one due to suicide because of terrorizing scenes and sounds experienced by a young girl.

In neither of the psychiatric and psychopharmacology textbooks, I could find any information about benzydamine as a hallucinogen, either alone or in combination with other drugs. When I asked for information for similar experiences to my colleagues, three of them sent me e-mails informing me about similar observations in their three patients; unfortunately none of them were published.

Although there is no previously published information about this hallucinogenic and deteriorating effect of benzydamine in a psychotic young person, physicians including orthopedist, dermatologists etc planning to prescribe benzydamine to their patients should concern and must take at least a brief anamnesis for previous or ongoing psychotic disorder.

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