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Drug-Induced Aseptic Meningitis, Sensorineural Hearing Loss and Vestibulopathy

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ABSTRACT

We report clinically rare and serious adverse reactions that occurred after the co-administration of ranitidine, ibuprofen and ciprofloxacin: completely reversible aseptic meningitis and irreversible bilateral sensorineural hearing loss, tinnitus, and vestibulopathy. Recurrent urinary inflammations treated with antibacterials, classic familial migraine, and allergy to trimethoprim-sulfamethoxazole and chromium were favourable predisposing factors for the adverse event in this patient. A close chronological relation between administration of drugs (especially ibuprofen) and adverse reactions was noted. No evidence of infection and/or autoimmune disease was found. The mechanism of these serious events may be explained as a hypersensitive reaction affecting the meninges and, partially, cochlea.

Key words: ranitidine, ibuprofen, ciprofloxacin, drug interactions, aseptic meningitis, deafness

Introduction

Aseptic meningitis (AM), with or without other drug-induced neurological disorders, has been the subject of several reviews^{1–4}. We report a case of drug-induced AM with ototoxic disturbances following the simultaneous use of a nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, a histamine blocker ranitidine, and a fluorinated quinolone antibiotic ciprofloxacin (CPFX).

Case Report

The represented study followed principles in the Declaration of Helsinki⁵. A 48-year-old-woman, mother of two children, body mass 21.5 kg/m², was suffering from frequent tonsillitis, classic familial migraine and urinary tract infections, and was allergic to chromium (occupational dermatitis) and trimethoprim-sulfamethoxazole (dermatitis medicamentosa).

She was hospitalized due to a 5-day lasting fever (to 38°C) and dysuria, which were treated *per os* with amoxicillin-clavulanate (Pliva, Zagreb, Croatia) and paracetamol (Lek, Ljubljana, Slovenia) (1875 and 1000 mg/daily, respectively). At admission, she was febrile, conscious

and cooperative. Physical and neurological examinations were without other particularities. Blood pressure was 155/80 mm Hg, and heart rate 100 beats/min.

Laboratory tests disclosed neutrophilic leukocytosis (leukocytes 13.2x10³/μL, segmented neutrophils 85%) without eosinophils, erythrocyte sedimentation rate of 50 mm/h, raised C-reactive protein (32 mg/L), IgG 18.7 g/L, fibrinogen 4.3 g/L, plasminogen activator inhibitor-1 4.36 mL, angiotensin-converting enzyme 65 mg (ref. value: 8–52), anti-streptolysin O titre (ASO) 1:166 Todd u, and decreased level of C3 complement component (0.8 g/L). Free thyroxin (FT4-RIA) was raised to 105.9 nmol (ref. value: 58–61). Human leukocyte antigens were -A2, -A24, -B17, -B35, -DR3, -DR11, -DQ2, -DQ3. Other components of the hemogram, routine chemistry, and tests for enzymes, proteins and lipoproteins, coagulation, hemostasis, autoimmune diseases and disorders of the immune system (Antinuclear Antibody, Anti-DNA Antibody test) were normal. Serology against *Brucella melitensis*, *Chlamydia psittaci*, *Borrelia burgdorferi*, *Treponema pallidum* and *Toxoplasma gondii* was negative. Routine urinalysis showed lightly turbid, alkaline (>pH

7) urine that was positive for nitrate, protein and bacteria, and negative for glucose and ketones. Microscopic examination of sediment showed 35 leukocytes, many epithelial cells and bacteria. Bacterial cultures from blood and urine were sterile. Chest radiography, abdominal ultrasound, ophthalmological and gynaecological examinations were normal.

The first two days, she received ibuprofen (Belupo, Koprivnica, Croatia) (2x400 mg) and ranitidine (Pliva, Zagreb, Croatia) (1x300 mg) orally. On the third day, CPMX (Pliva, Zagreb, Croatia) (2x500 mg orally) was prescribed due to presumed . At nightfall, the patient complained of diffuse and painful »burning« dysesthesia of

the whole body, followed by headache, photophobia, neck stiffness, nausea and drowsiness. On the 4th day, EEG was moderately dysrhythmic. Routine and special skull radiography, and computed tomography of the head were unremarkable. Magnetic resonance imaging of the brain, with and without gadolinium, showed hyperintensity on T2-weighted images in both labyrinths, markedly on the left. Cerebrospinal fluid (CSF) analysis showed lymphocytary pleocytosis, and dysfunction of the blood-brain barrier (BBB) with definite intrathecal IgG synthesis (Table 1). Ibuprofen and ranitidine were discontinued.

The day after, the meningeal syndrome completely regressed. However, the patient was atactic. She com-

TABLE 1
CEREBROSPINAL FLUID ANALYSIS OF PATIENT

Characteristics	1.st CSF	2.th CSF (six months after)
Appearance	Like water	Like water
Total protein (mg/dl)	125	31
Total cell count (WBC/ μ l)	118	3
Lymphocytes (%)	62	Nd
Activated lymphocytes (%)	6	Nd
Plasma cells (%)	1	Nd
Plasmacytoides lymphocytes (%)	3	Nd
Neutrophils, segmented (%)	4	Nd
Monocytes (%)	16	Nd
Activated monocytes (%)	6	Nd
Macrophages (%)	2	Nd
Glucose (mg/dl)	57	52
Concomitant serum glucose	107	91
Lactate (mmol/L)	2.51	1.8
Immunoglobulin G (g/L)	0.222	0.025
Immunoglobulin G quotient	13.3	3.0
Albumin (g/L)	0.62	0.18
Albumin, serum (g/L)	51.3	Nd
Albumin quotient	12.1	4.4
Intrathecal Immunoglobulin G synthetic rate	1.1	Nd
Blood CSF barrier function	74	143
Oligoclonal banding	negative	negative
CSF bacterial cultures*	negative	negative
Antibodies to major DNA and RNA viruses**	negative	negative
Antibodies to <i>Borrelia burgdorferi</i>	negative	negative
VDRL	negative	negative
Cryptococcal antigen test	negative	negative

*the presence of *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, B- and D-group Streptococci, *Listeria monocytogenes*, *Mycobacterium* was excluded.

**DNA viruses: HSV1, HSV2, VZV, CMV, EBV, HHV-6, PARVO B19; RNA viruses: PARAINFL. 1-3, PAROTITIS, MORBILLI, INFLUENZA A and B, RUBELLA, RSV, HIV
Immunocomplexes were not investigated

plained of bilateral deafness with tinnitus. An audiogram showed bilateral sensorineural hearing loss (SNHL), with threshold of hearing around 25–35–30 dB (right), and 50–55–50 dB (left). Acoustic reflex was positive. On the left, we identified tinnitus (frequency 8000 Hz, intensity 55 dB), absence of vestibular reflex, and abnormal brainstem auditory-evoked potentials. Horizontal nystagmus appeared by looking to the left. Visual and somatosensory-evoked potentials were normal. Cutaneous immunofluorescence biopsy showed normal findings. CPF_X administration was stopped.

The patient was discharged after 10 days. Neurological examination showed bilateral SNHL with tinnitus. She received orally betahistine (Pliva, Zagreb, Croatia) (2x12 mg/day).

Six months later, she was examined in a day hospital because of arthromyalgias, headache, vertigo, bilateral deafness and squeaky tinnitus on the left. Laboratory tests were normal, except ASO, which continued to be 1:166 Todd u. A second lumbar tap showed CSF without meningeal inflammatory signs (Table 1). An audiogram verified SNHL with hearing threshold among 35–40–40 dB (right), and 40–45–45 dB (left). On the left, tinnitus (frequency 4000 Hz, intensity 50 dB) and vestibulopathy were confirmed.

The patient received intramuscularly diclofenac (Pliva, Zagreb, Croatia), (1x75 mg/day during 5 days), and did not develop adverse reactions.

Discussion

The clinical picture, as described, is based on a close chronology of administration/discontinuation of drugs, and development/partial *restitutio ad integrum* of disorders.

The drugs administered, in the recommended therapeutic range, were paracetamol, amoxicillin-clavulanate, ranitidine, ibuprofen and CPF_X. Although amoxicillin-clavulanate is rarely responsible for AM⁶, the first two drugs did not cause adverse effects. AM and rapid onset of deafness developed only after the simultaneous administration of the last three drugs. Ranitidine very rarely causes AM⁷, and does not significantly alter the bioavailability of CPF_X⁸. Ibuprofen is the most common cause of AM in monotherapy (32 published reports). Ibuprofen-induced AM is often recurrent and frequent in patients with collagen (vascular) diseases³. Davison et al. report a case with bilateral SNHL and tinnitus in ibuprofen-induced AM, where ibuprofen was taken every six hours for three months. The disturbances disappeared after drug cessation⁹. Asperilla and Smego report a case of eosinophilic meningitis associated with orally taken CPF_X¹⁰.

Interactions between ranitidine/ibuprofen and ranitidine/CPF_X are weak and of limited clinical significance¹¹. Although there is extensive documentation of the *in vivo* and *in vitro* interactions between quinolones and NSAIDs,

minimal documentation of patients in whom a correlation between central nervous system toxicity and concomitant administration of the two classes of drugs is available. Moreover, this type of potentially very serious interaction is not mentioned in the package inserts of the marketed quinolones¹². CPF_X was shown to interact with ibuprofen *in vitro* and *in vivo*, but less than with other NSAIDs¹³. Ibuprofen prolongs CPF_X half-life in the serum, enhances its extravascular diffusion into tissues, modifies its renal excretion, and allows its passage through the BBB, thus potentiating its neurotoxicity¹⁴. As an inhibitor of CYP-mediated metabolism, CPF_X may be responsible for the toxicity of co-administered ibuprofen by decreasing its clearance⁸.

Correct identification of the causative drug responsible for AM and SHNL in our patient is uncertain. The incriminated drug(s) could be ibuprofen and/or ranitidine, as the patient had never taken them before, and the AM completely regressed after their cessation. Absence of suggestive biological findings (pointing to infectious etiology or rheumatological/connectivitis disturbances) suggests an allergic/idiosyncratic reaction, which is presumably a hypersensitivity reaction type III to ibuprofen with a secondary, local inflammation process (vasculitis) restricted in the meninges³. Increased serum concentration of FT4-RIA might also suggest a pharmacologically-induced barrier dysfunction¹⁵. We assume that bilateral partial deafness was caused by a simultaneous inflammatory dysfunction of cochlear vessels endothelium. Gender, age, migraine, recurrent urinary inflammations, and particularly allergy to trimethoprim-sulfamethoxazole, might all contribute as predisposing factors for the adverse reactions in this patient.

CPF_X is probably not an offending agent for SNHL and vestibulopathy, as the drug *in vitro* is harmless to the sensory organs for hearing and equilibrium in the inner ear¹⁶. Subsequent administration of diclofenac did not cause any adverse reactions. Thus, the neurotoxic adverse reactions of ibuprofen do not contraindicate the use of other NSAIDs.

With this case report, we wanted to draw attention on the possibility of AM onset as a severe consequence in therapy with ibuprofen – alone or in combination with other drugs. Re-administration of this drug to the patient would be a method of choice for confirmation of the diagnosis. However, this was not done as we considered this procedure as non-acceptable ethically.

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ASEPTIČKI MENINGITIS, PERCEPTIVNA GLUHOĆA I VESTIBULOPATIJA IZAZVANI LIJEKOVIMA. PRIKAZ BOLESNIKA

SAŽETAK

Prikazuju se klinički rijetke i ozbiljne nuspojave izazvane primjenom ranitidina, ibuprofena i ciprofloksacina: potpuno povratni aseptički meningitis i nepovratna obostrana perceptivna gluhoća, tinitus i vestibulopatija. Opetovane upale mokraćnih putova liječene antibioticima, klasična familijarna migrena te alergija na trimetoprim-sulfametoksazol i kromove boje bile su predispozicijski čimbenici za nastup tih nuspojava u bolesnice. Uska kronološka spona bila je opažena između primjene lijekova (naročito ibuprofena) i nuspojava. Nisu bile uočene posebnosti infekcija i/ili autoimunskih bolesti. Mehanizam tih ozbiljnih nuspojava može se objasniti kao reakcija preosjetljivosti koja obuhvaća moždane ovojnice i, djelomično, pužnicu.