Dual drug-induced aseptic meningoencephalitis: More than a suggestion

Mario Coletti Moja, Giovanna Riva and Edoardo Catalfamo

Abstract
We present the case of a patient with a first single episode of a dual drug-induced aseptic mening (DIAM) due to amoxicillin and ibuprofen and a short review of updated literature. A 76-year-old man was admitted to our hospital with slowness and confusion following a dental and gingival inflammation treated with oral amoxicillin 500 mg bid and ibuprofen 600 mg tid for 1 week. His mental state and higher functions abruptly worsened after therapy increase leading to hospitalization. Both the drugs were stopped and the patient improved rapidly within 2–3 days and was released asymptomatic after a week. On the basis of this temporal relationship with a comprehensive negative neuroimaging and laboratory testing for viral, bacterial, and mycobacterial micro-organisms, a DIAM by amoxicillin and ibuprofen was diagnosed. We support the hypothesis that this dual therapy was causative because of the progressive onset of central nervous system symptoms starting at a low amoxicillin dose with a high ibuprofen intake and that this sort of chemical meningoencephalitis was mostly due to the pharmacokinetic of amoxicillin after its dose increase. To our knowledge, this is the first documented publication of a severe first episode of DIAM with predominant higher function involvement caused by these two drugs commonly used together, amoxicillin and ibuprofen.

Keywords
Amoxicillin, aseptic meningoencephalitis, dental inflammation therapy, dentistry, drug toxicity, ibuprofen, neurology

Date received: 11 January 2021; accepted: 6 May 2021

Introduction
Drug-induced aseptic meningitis (DIAM) is a rare cause of adverse reaction to drug therapy. It is a rare idiosyncratic event which may occur after local or systemic drug administration and in which any other causes of meningoencephalitis were ruled out. Moreover, DIAM is a relatively uncommon and probably underestimated diagnosis, and only about 200 cases have been reported in the literature so far.1 Clinical picture of DIAM can mimic a viral subacute infection and includes meningeal (headache, neck stiffness, Kernig and Brudzinski signs) and brain damage symptoms (slowness, somnolence, seizures) with a marked predominance of the former ones as reported in the literature. Fever, if present, is usually mild and inflammatory indexes as C reactive protein (CRP) are low. Many kinds of drugs are involved in DIAM and their number is continuously increasing. The most commonly involved drugs are nonsteroidal anti-inflammatory drugs (NSAID) as ibuprofen2 which is a non-selective inhibitor of cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2). Pharmacokinetic properties of ibuprofen, especially its short plasma half-life of elimination and the lack of development of pathologically related metabolites, are in support for the view that these pharmacokinetic and notably metabolic effects of ibuprofen favour its low toxic potential. Nevertheless, ibuprofen at high doses can exert its toxicity on various cellular processes that are affected by the inhibition of the COX pathway or can act as a hapten with tissue proteins and cause a local inflammatory process. Other frequently reported offending therapies include many antimicrobials, such as co-trimoxazole, trimethoprim-sulfamethoxazole, metronidazole and isoniazid and the antibiotic compounds ciprofloxacin and cephalaxin among cephalosporins and amoxicillin among penicillins.3,4 Amoxicillin has been in use since the 1970s; it is the most widely used...
intravenous immunoglobulin and radiographic agents have
against the T3 receptor and, pan T-cell antibodies and even
thidine, carbamazepine, vaccines, monoclonal antibodies
netic resonance imaging (MRI) was normal too. Patient was
disappeared in the following days. A brain Gadolinium mag-
bursts lasting 3–4 s, predominantly rostrally that gradually
marked slowing of the basal rhythm with diffuse theta-delta
formans) was negative. No brucellosis or Lyme disease risk
Cryptococcus neo-
cella-zoster virus, human parechovirus,
cytomegalovirus, Haemophilus influenzae, Escheria coli,
lactiae, Neisseria meningitidis, Listeria monocytogenes,
Streptococcus pneumoniae and
gaga-
CSF cultures (namely
screening with multiplex polymerase chain reaction (PCR)
centration (82 mg/dL). CSF routine cultures and a full viral
transaminase (96/mm3), a normal glucose level and elevated protein con-
seizures, myoclonus, ataxia and psychosis were absent.

**Case report**

A 76-year-old man with a negative history of any allergies or
auto immune pathology started amoxicillin 500 mg bid and
ibuprofen at high dose 600 mg tid for an aching dental and
gingival infection with no detectable local abscess with
fever; after 5–7 days he started feeling dizzy and then was
suffering from somnolence, amnesia, ideative and perceptive
slowing and was admitted to the hospital emergency room
(EH). Blood values were normal at admittance and did not
change during the time spent in hospital (creatinine = 1.16
mg/dL, glomerular filtration rate = 71 mL/min, aspartate transaminase = 20 U/L, alanine transaminase = 20 U/L)
except C-reactive protein = 6.7 mg/L, white blood cell =
12.07 × 10E3 c/μL with neutrophils 9.36 × 10E3 c/μL.
Computed tomographic scan of the brain was normal. Based
on an oral inflammation clinical picture, amoxicillin was
increased to 1 g tid, clavulanic acid was added and the patient
was released. The next day his clinical picture worsened
abruptly leading to a severe higher brain functions impairment
with apraxia, mental slowing and marked somnolence
with profound asthenia and hyporexia. Absent were clear
meningitis symptoms (headache, meningism, stiffness)
while a subtle myalgia was later reported during hospitaliza-
tion. The patient was then admitted to EH with blood values
similar to the day before and his neurological picture was
unremarkable, with no headache or meningism. Also fever,
seizures, myoclonus, ataxia and psychosis were absent.
Cerebrospinal fluid (CSF) showed mononuclear pleocytosis
(96/mm3), a normal glucose level and elevated protein concentration (82 mg/dL). CSF routine cultures and a full viral
screening with multiplex polymerase chain reaction (PCR)
assay for conventional meningoencephalitis from primary
CSF cultures (namely Streptococcus pneumoniae and a-
laetiae, Neisseria meningitidis, Listeria monocytogenes,
Haemophilus influenzae, Escherichia coli, cytomegalovirus,
teveroviruses, herpes simplex virus type 1, 2 and 6 and vari-
cella-zoster virus, human parechovirus, Cryptococcus neo-
formans) was negative. No brucellosis or Lyme disease risk
was reported. Electroencephalogram (EEG) showed a
marked slowing of the basal rhythm with diffuse theta-delta
bursts lasting 3–4 s, predominantly rostrally that gradually
disappeared in the following days. A brain Gadolinium mag-
netic resonance imaging (MRI) was normal too. Patient was
then treated symptomatically with ceftriaxone 1 g bid for the
dental infection and both amoxicillin and ibuprofen were
promptly stopped. His symptoms resolved within 72 h after
drugs discontinuation with a normalization of CRP value
(1.6 mg/L). Prior and during this episode, he did not take any
other drug. In the following weeks, CSF cultures were nega-
tive and no causative microorganism was identified and
patient was free from toothache. At a 9-month follow-up the
patient is asymptomatic.

**Discussion**

Diagnosis of DIAM in our patient was based on published cri-
tera: a temporal relationship with drug intake, CSF pleocyto-
sis, negative extensive microbiological tests, rapid complete
resolution after drug discontinuation,6 positive rechallenge
was not present in our case because after the amoxicillin dos-
age increase clinical picture clearly worsened and led to the
suspicion of a drug-related encephalitis. Any concomitant
abnormalities in renal or liver function were excluded.
Detailed anamnesis is always essential to have a DIAM diag-
nosis, because it is particularly related to any medication used
immediately prior to the appearance of symptoms of central
nervous system (CNS) impairment and it is crucial establish-
ing a temporal relationship between the administration of the
drug, the onset of clinical symptoms and the rapid resolution
of the syndrome after drug withdrawal.7 As described in the
literature, no gender predominance is reported in DIAM, mean
age of reported cases is 60 years (29–86) with a latency time
ranging from 12 h to 4 days from drug intake and a shorter
resolution time in younger subjects but usually seen in
3–4 days. All the patients had CSF pleocytosis, 50% of the
cases lymphocytes and 50% mononuclear while the 100% had
an elevated protein and normal glucose amount. Of course
extensive CSF cultures and viral PCR are negative as neces-
sary criteria for diagnosing DIAM. As for our patient, we
believe that both amoxicillin and ibuprofen could have caused
our patient’s DIAM through a synergic effect of the two drugs
because the first CNS symptoms were present with a high ibu-
profen and a medium amoxicillin dose even if the marked
worsening after the dose increase of amoxicillin makes very
probable that the former could be the precipitating factor and
most effective drug. Noteworthy in our case is the fact that the
predominant clinical deficits were mostly only cortical and
they fluctuated in some days from aspecific slowness with
somnolence to apathy and ideative apraxia after 10 days at a
full amoxicillin dose while meningitis symptoms were always
mild and fever absent. Recovery was fully complete after
3–5 days from release and patient blood values prompt long-
lasting normalization with CRP value 1.6 mg/L make a false
negative CSF culture/PCR very unlikely. Moreover, the
patient was on ceftriaxone therapy only a few days after
release with no further infection symptoms. Physiopathological
mechanisms of DIAM are little known and are partially
described. They may be different according to the causing
agent and the situation of every single patient. Two types of mechanisms are commonly proposed for DIAM: a direct chemical irritation of the meninges or a delayed hypersensitivity response while an IgE-mediated mechanism has never been reported. We instead suggest that since amoxicillin absorption rate appears to be saturable, this results in a non-linear increase and a later maximal time for higher doses. Increasing the dose results in a larger percentage of free minimal inhibitory concentration (MIC) due to this delayed absorption, despite the non-proportional increase in maximal concentration. However, a higher dose increases the risk of adverse events, and a shorter interval between doses leads to a larger free MIC as well. The dose/frequency balance should be optimal to get the most antimicrobial efficacy and the lowest risk of adverse events. In fact, DIAM CSF pattern could be related to this pharmacodynamic model. Clinicians should be cautious about prescribing ibuprofen or oral amoxicillin regimens at high doses as well as switching from twice to three times a day and this fits with our patient’s clinical course. The absence of evident meningitis symptoms could be due to a minimal or totally absent inflammation of the meninges, as suggested by CSF pattern, with a predominant higher functions imbalance directly related to drugs effect and promptly withdrawing after therapy discontinuation.

Conclusion
DIAM is a rare condition and can be a difficult diagnosis, commonly underrated in polytherapies. A detailed anamnesis, particularly focused on drugs used immediately prior to the onset of CNS impairment, is essential for DIAM diagnosis, even when a number of drugs are prescribed. In all previous literature cases of amoxicillin-related DIAM, a documented positive rechallenge since the first episode of aseptic meningitis is reported, ranging from 2 to 7 episodes, because DIAM was not attributed to amoxicillin at first, as exhaustively reviewed in published papers. Conversely, in our patient the amoxicillin dose increase led to a rapid and marked clinical worsening making rechallenge unnecessary for the diagnosis. We believe that this could be a further strong issue in diagnosing DIAM even at the very first episode. We suggest that non-linear absorption pharmacokinetics of amoxicillin should be kept in mind to avoid serious consequences related to dose regimens and leading to harmful clinical breakthroughs mostly when other potentially harmful drugs (ibuprofen and NSAID) which are known to cause DIAM are prescribed together. This could be kept in mind by physicians who often prescribe this kind of medications in their daily practice, dentists and otorhinolaryngologists above all, who daily deal with patients’ oral and dental pathologies and inflammatory diseases.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval
Our institution does not require ethical approval for reporting individual cases or case series.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent
I have obtained the necessary written patient informed consent to publish patient information.

ORCID ID
Mario Coletti Moja https://orcid.org/0000-0002-8452-683X

References
1. Moris G and Garcia-Monco JC. The challenge of drug-induced aseptic meningitis revisited. JAMA Intern Med 2014; 174(9): 1511–1512.
2. Desgranges F, Tebib N, Lamy O, et al. Meningitis due to non-steroidal anti-inflammatory drugs: an often-overlooked complication of a widely used medication. BMJ Case Rep 2019; 12; e231619.
3. Cascella C, Nausheen S and Cunha B. A differential diagnosis of drug-induced aseptic meningitis. Infect Med 2008; 25: 331–334.
4. Shahien R, Vieksler V and Bowirrat A. Amoxicillin-induced aseptic meningoencephalitis. Int J Gen Med 2010; 3: 157–161.
5. Huttner A, Bielicki J, Clements MN, et al. Oral amoxicillin and amoxicillin-clavulanic acid: properties, indications and usage. Clin Microbiol Infect 2020; 26: 871–879.
6. Meier JE, Smith KP and Meningitis I-AA. Ibuprofen-associated aseptic meningitis. J Pharm Pract 2006; 19: 113–123.
7. Yelehe-Okouma M, Czmil-Garon J, Pape E, et al. Drug-Induced aseptic meningitis: a mini-review. Fundam Clin Pharmacol 2018; 32(3): 252–260.
8. Periard D, Mayor C, Aubert V, et al. Recurrent ibuprofen-induced aseptic meningitis: evidence against an antigen-specific immune response. Neurology 2006; 67: 539–540.
9. de Velde F, de Winter BC, Koch BC, et al. Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakthroughs. J Antimicrob Chemother 2016; 71(10): 2909–2917.
10. Turk VE, Šimić I, Makar-Aušperger K, et al. Amoxicillin-induced aseptic meningitis: case report and review of published cases. Int J Clin Pharmacol Ther 2016; 54(9): 716–718.