Amoxicillin and amoxicillin plus clavulanate: a safety review

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Despite the considerable number of newer antibacterials made available over the past decades, amoxicillin, alone or in combination with clavulanic acid, still accounts among the most widely used antibacterial agents. Although they are often considered ‘twin drugs’, they are different both in terms of antibacterial activities and of safety profile. It is well documented that the clavulanate component may cause adverse reactions by itself, thus exposing patients to further, and sometimes undue, risks. Although amoxicillin/clavulanate should be considered as an alternative agent only for the treatment of resistant bacteria, evidence shows that it is often used also when a narrow-spectrum antibiotic would have been just as effective. This prescription habit may have serious consequences in terms of patients’ safety, as well as in terms of the development of bacterial resistance.

Keywords: adverse drug reactions, amoxicillin, clavulanic acid, β-lactams

1. Introduction

Infections still represent a common cause of morbidity and mortality worldwide, with acute respiratory tract infections (RTIs) accounting among the most prominent reasons for hospital admissions and increased economic burdens for national health systems [1]. Despite the considerable number of newer antibacterials made available over the past decades, β-lactam antibiotics are still the most used antibacterials all over the world. The first β-lactams were licensed in the 1950s (penicillin G and V) and presented substantial inconveniences, most notably a limited range of activity, a short half-life, and the administration route had to be parenteral. The development of a semisynthetic pathway for their production in the 1960s led to the creation of newer penicillins, with significant improvements in their range of activity. Namely, ampicillin and amoxicillin (AMX) were the two most striking innovations, effective not only in the treatment of upper and lower RTIs but also for urinary tract, soft-tissue and skin infections.

AMX, in particular, is a moderate-spectrum, semisynthetic β-lactam active against a wide range of Gram-positive and a limited range of Gram-negative organisms [2]. It was marketed in 1972, and still remains the most commonly utilised drug in this class because its oral absorption is better when compared with other β-lactam antibiotics [3].

Unfortunately, during the past decades, an increasing number of bacteria have become resistant to antibiotics, making bacterial resistance one of the world’s most pressing public health problems. β-Lactamase production is one of the most common mechanisms of bacterial resistance; these enzymes, that cleave the β-lactam ring, can be produced by several Gram-positive organisms (including Staphylococci spp.), Gram-negative organisms (Escherichia coli, Neisseria gonorrhoeae, Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas and Klebsiella spp.), and anaerobic organisms (Bacteroides spp.) [4,5]. To overcome this problem, in the 1970s, a new area of
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research was focused on identifying compounds able to inhibit β-lactamase, and in 1972 clavulanic acid (CA) was identified. CA is structurally related to penicillins; it prevents inactivation of antibiotics, thus increasing their effectiveness when combined [6]. The association of amoxicillin/clavulanate (AMC) was first marketed in 1981, and it is the only penicillin combined with a β-lactamase inhibitor available in oral formulation [7].

This review examines data available in literature for AMX and AMC to highlight differences in their safety profile.

2. Pharmacological properties

2.1 Mechanism of action

β-Lactams interfere with the synthesis of peptidoglycan, an important component of Gram-positive bacterial cell walls. The final transpeptidation step in the synthesis of the peptidoglycan layer is facilitated by transpeptidases (penicillin-binding proteins). The β-lactam nucleus permanently binds to the penicillin-binding proteins, preventing the final crosslinking (transpeptidation) between the linear peptidoglycan polymer chains and disrupting cell wall structure [3].

CA binds irreversibly with β-lactamase, preventing it from inactivating β-lactam antibiotics [8]. Consequently, when combined, it broadens the range of activity of AMX to include AMX sensitive and β-lactamase-producing bacterial strains [8-9]. This property has become increasingly important for respiratory pathogens, most notably H. influenzae and M. catarrhalis, to acquire the capacity to produce β-lactamase [10,11].

2.2 Available formulations and dosage regimens

AMX and AMC are available in a range of formulation and dosage combinations for parenteral and peroral delivery [12].

Over the years, several formulations of AMC have been developed and the ratio of AMX to CA has been varied to reflect new prescribing guidelines for the treatment of more severe infections or those caused by resistant microorganisms. The following ratios of AMX:CA combinations are available on the market for oral use: 2:1 (250/125 mg), 4:1 (125/31.25, 250/62.5 or 500/125 mg) and 7:1 (200/28.5, 400/57 or 875/125 mg). In addition, a new high-dose formulation (600/43 mg, 14:1 ratio) has been approved in the US for twice-daily administration [12].

2.3 Pharmacokinetic

Both AMX and CA are well absorbed in the gastrointestinal (GI) tract after administration of oral suspension or tablet formulations. However, differences in the extent of AMX absorption in various regions of the GI tract have been observed, with major absorption in the upper small intestine and poor colonic absorption [13-16]. The oral bioavailability of AMX is about 70 – 90% and maximum serum concentrations occur in 60 – 90 min after administration [17]. CA shows more variable oral bioavailability (60.0 ± 23.1% on average, with a range between 31.4 and 98.8%) [18].

Although AMX is excreted unchanged in the urine in 6 h after administration (50 – 80%), CA undergoes more extensive liver metabolism, possibly by hydrolysis followed by decarboxylation, with only 20 – 60% of unchanged drug being excreted in the urine in 6 h after administration [19-21].

The mean elimination half-lives of AMX and CA are 1 h each. Both drugs are well distributed into body tissues and extracellular fluids, with low binding to plasma proteins (18 – 25%) [19].

2.4 Clinical use

Because AMX is well absorbed after oral administration, it is extensively used in out-patient settings, primarily in the treatment of community-acquired RTIs; furthermore, together with penicillin V, it is the first-choice antibiotic for the treatment of Streptococcus pyogenes infections [10,22,23]. It is also combined with other medications for Helicobacter pylori eradication [24].

AMC is suggested for the treatment of suspected or documented Gram-negative infections caused by β-lactamase-producing strains of H. influenzae, N. gonorrhoeae, E. coli, M. catarrhalis and Proteus, Klebsiella and Bacteroides species. It is also a first-choice antibiotic in clinical situations in which there is increased development of β-lactamase-producing organisms, as for the treatment of otitis media, sinusitis, bronchitis, urinary tract infections and skin and soft tissue infections [25]. AMC has no clinical utility against Pseudomonas or methicillin-resistant Staphylococcus aureus, owing to its negligible in vitro activity. Moreover, it is important to underline that the Streptococcus pneumoniae mechanism of resistance is not owing to β-lactamase production, and, therefore, AMC does not add efficacy to the use of AMX alone.

3. Safety

AMX and AMC are well tolerated; the most frequently reported adverse events for both are GI disturbances, including diarrhoea, nausea and vomiting, although published studies indicate some differences on their safety profiles [26-28].

3.1 Gastrointestinal tolerability

AMX and AMC have been associated to mild/moderate GI side effects, such as nausea, vomiting, cramping (prevalence 3 – 6%), or diarrhoea (4 – 15%) [29].

The good oral absorption of AMX makes it better tolerated at the GI level compared with other β-lactams. For instance, because AMX is more completely absorbed than ampicillin, a smaller amount of AMX remains in the intestinal tract, thus provoking less diarrhoea than ampicillin [26]. Evidence available from both clinical trials and postmarketing studies indicates a higher frequency of GI events, including transient diarrhoea, vomiting and nausea, linked to AMC than to AMX use [27-28]; the frequency of these events seem to be related to the dosage of CA [13]. Moreover, five clinical trials reviewed by Bax showed a small reduction in the frequency of diarrhoea when b.i.d. AMC dosage (875/125 mg) was
patterns may also occur. The onset is generally hepatocellular or mixed cholestatic and hepatocellular liver injury than for AMC in two different studies. The difference in incidence rates may be owing to several factors, including the type of study, degree of liver injury, age of study population and so on.

Some evidence suggests a direct responsibility of the CA component in the adverse hepatic events attributed to AMC. In fact, AMX alone provided a sixfold lower incidence of liver injury than for AMC in two different studies. Moreover, despite its longer use, only four published case-reports of AMX-induced liver injury are available. Furthermore, some published case-reports describe patients who had experienced liver injury with AMX but did not have any hepatic event after switching to AMX, although other reports described positive rechallenge in patients with AMX-induced hepatotoxicity. Further confirmation is derived from reports of liver damage that occurred in patients treated with combination of CA with tircacillin. AMC-liver injury typically occurs as cholestatic hepatitis; hepatocellular or mixed cholestatic and hepatocellular patterns may also occur. The onset is generally delayed from several days up to weeks after starting the therapy (8.9 days after the first administration on average, range 1 – 48 days), but might also occur up to 8 weeks after its cessation. Such a feature is uncommon in drug-induced liver injuries and makes diagnosis more difficult. Interestingly, it has been reported that hepatocellular damage is more frequent in patients < 55, and after shorter treatments; conversely, older patients, who have also had prolonged AMC therapy, develop cholestatic/mixed type damage.

### 3.2 Liver tolerability

Among antibiotics, AMC is the one most frequently associated with liver injury (Table 1), as well as the most frequently prescribed drug leading to hospitalisation for drug-induced liver disease. AMC-related liver injury was first reported in 1988, and since then > 200 cases have appeared in literature. Although transient elevation of serum transaminases is not uncommon after AMC-therapy, hepatic injuries are rare, with an incidence ranging from 1 to 1.7 per 10,000 users. Other studies estimated a much lower risk, with an overall rate of < 1 in 100,000 persons exposed. The difference in incidence rates may be owing to several factors, including the type of study, degree of liver injury, age of study population and so on.

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A slower drug elimination related to advanced age and its concomitant retention in the body would, in turn, allow a prolonged exposure of the bile duct cells to the drug metabolite through canalicular excretion, which may trigger an immune response against haptenised duct cell proteins and a periductular inflammatory reaction. Overall, advanced age and male gender seem two recognised risk factors for AMC-induced liver injury. The combination of advanced age and long-term therapy (≥ 10 days) resulted in the greatest absolute risk of developing acute liver injury during AMC therapy (> 1/1000 users). Nevertheless, Thomson et al. did not find a significant correlation between the duration of therapy and hepatitis. Furthermore, a population-based case-control study did not confirm a relation with age, sex or long-term use, although suggesting a dose-dependent mechanism.

AMC-induced hepatitis is normally reversible after drug withdrawal, with a wide variability in the duration of symptoms (1 – 8 weeks). However, a prospective case-series involving 69 patients estimated an unfavourable outcome (death, liver transplantation or persistent liver damage) in 7% of AMC-related hepatotoxicity. Moreover, an analysis from a Spanish hepatotoxicity registry showed that AMC was the first causative drug of chronic liver injury; it is noteworthy that chronicity was more common with cholestatic reactions than with hepatocellular or mixed.

Although the mechanism of AMC-related hepatitis remains unclear, its frequent association with hypersensitivity manifestations (such as skin rash or hypereosinophilia) suggests an immunological mechanism, possibly related to selected human leucocyte antigen (HLA) haplotypes. In particular, HLA-DRB1*15 and -DQB1*06 alleles seem to be involved in the development of a cholestatic/mixed pattern in drug-induced liver injury; on the other hand, DRB1*07 and DQB1*02 alleles seem to be protective. These findings support the general notion of the allergic-based mechanism of cholestatic/mixed hepatotoxicity. More recently, the combined deficiency of alleles M1 and T1 in glutathione S-transferase genes has been found to play a role in susceptibility to AMC-induced liver injury.

### 3.3 Allergic reactions

Allergic reactions to β-lactams occur in 0.7 – 8% of treated patients. These effects have for long time been related to the sensitising effect of the benzylpenicillloyl moiety, which is formed when the β-lactam ring is cleft. However, the contribution made by the chemical structure of the AMX side chain is gaining importance as a part of the epitope responsible for the specificity of the response. The contribution of CA to IgE-mediated reactions seems to be modest, because this molecule has proven to be by itself poorly immunogenic and allergenic. This hypothesis is also supported by two large postmarketing studies, showing a similar reporting rate for both AMX and AMC, in spite of the wider use of the latter. Conversely, two spontaneous
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Table 1. Adjusted odds ratio for acute liver disorder and current use of antibiotic.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Adjusted odds ratio (95% CI)</th>
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<tbody>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>94.8 (27.8 – 323)</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>15.3 (2.9 – 80.7)</td>
</tr>
<tr>
<td>Tetraciclines</td>
<td>6.2 (2.4 – 15.8)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>6.1 (0.8 – 45.9)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>5.3 (1.4 – 45.9)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>2.9 (0.6 – 14.1)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1.7 (0.6 – 4.8)</td>
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Adapted from De Abajo et al. [35].

reporting studies have found consistent differences, concluding that AMX causes more skin reactions than AMC [27,28]. One of them showed that, despite the higher frequency of AMX-induced cutaneous reactions (82 versus 76% of spontaneous reports), AMC was more frequently involved in non-IgE-mediated hypersensitivity reactions, and in particular Steven–Johnson Syndrome (SJS) (reporting odds ratio 2.6 versus 0.64) [28]. This apparently controversial evidence could be explained by the two different mechanisms involved. In particular, although the higher frequency of AMX-related skin reactions is mainly caused by hypersensitivity reactions to the penicillin ring component, an ‘immunologic idiosyncrasy’ involving HLA-class-II antigens has been supposed for AMC. This hypothesis originates from the observation that in some reports CA-induced hepatitis occurred together with cutaneous adverse reactions, and in particular one patient developed fatal SJS after severe hepatotoxicity [43,52,71].

3.4 Safety in special population
3.4.1 Children
Most frequently reported AMC-induced adverse events in children were mild GI disturbances (< 5%); as for adults, diarrhoea is largely attributed to the CA component [60]. The incidence of diarrhoea is significantly lower for b.i.d. than with t.i.d. regimen (6.7 – 9.6 versus 10.3 – 26.7%, respectively) [72]. Moreover, a study on out-patient children showed a statistically significant increased risk of antibiotic-associated diarrhoea related to AMC use compared with all other antibiotics combined (RRr.43 CI 95%:1.40 – 4.21; p = 0.003). The relative risk rose to 3.5 (1.89 – 6.46) in children aged < 2 years [73].

No serious adverse events and a low total incidence of events (3.6%) were reported during postmarketing surveillance of 3048 children aged ≤ 14 years with acute otitis media who received AMC 300 – 450 mg/day in three divided doses [72].

3.4.2 Elderly people
With the exception of AMC-hepatotoxicity, available data do not indicate an increased risk of developing adverse reactions due to AMX or AMC treatment with the increase of age [49,58]. Nevertheless, because the two drugs are substantially excreted by the kidney, the risk may be greater in elderly patients, who are more likely to have impaired renal function. The common use of combinations of several medications in the elderly may also pose patients a higher risk of drug–drug interactions between either AMX or AMC and other drugs. Albeit, the risk of clinically relevant interactions is low; three case-reports suggested a possible relation between the decrease in vitamin K-producing flora of the intestine induced by AMC and the occurrence of bleeding complications in patients treated with warfarin [74-76].

3.4.3 Pregnant women
Penicillins as a class are generally considered safe for use in pregnancy; although both AMX and AMC cross the placenta to enter the foetal circulation and amniotic fluid, their use in pregnant women for the treatment of various infections has not, until now, produced recognised congenital malformations [77-79]. Furthermore, an expert review of published data on AMX use during pregnancy concluded that therapeutic doses are unlikely to pose a substantial teratogenic risk [80]. There are, however, no adequate studies showing its safety when administered to pregnant women. The FDA now classifies both AMX and AMC in the ‘B’ category (no adverse effects in well-controlled studies of human pregnancies with adverse effects seen in animal pregnancies or no adverse effects in animal pregnancies without well-controlled human pregnancy data available) [81]. Finally, both drugs are considered as usually compatible with breastfeeding [82].

4. Conclusions
The relative toxicity of AMX and AMC showed some significant differences. Liver toxicity is strongly related to AMC treatment, whereas AMX is only marginally implicated. The involvement of the CA component, which is significantly metabolised through the liver, has been confirmed by several case-reports and postmarketing studies. There is still a debate concerning the mechanism involved in such adverse reactions; the most frequently evoked is an ‘immunologic idiosyncrasy’ against the CA component. These immunogenic properties also explain, at least partially, the higher frequency in SJS occurrence with AMC, despite the overall higher number of cutaneous adverse reactions related to AMX. Finally, AMC is more frequently involved in GI disturbances than AMX, probably owing to the CA dosage.

5. Expert opinion
There is a growing body of evidence showing that AMX and AMC have different safety profiles, with an overall higher risk for AMC than AMX. In particular, the presence of CA may pose for a significant number of treated patients at an increased risk of liver toxicity and serious cutaneous reactions.
with clinically relevant consequences. It may be argued that the increased risk for AMC is counteracted by its broader range of antibacterial activity, which allows treatment of a wider range of pathogens, including β-lactamase-producing strains. Nevertheless, because AMX and AMC are used indifferently for the same indications in clinical practice, this advantage is often neutralised; moreover, AMC use has been reported to induce the selection of strains producing penicillinase, thus leading to an increased risk of clinical resistance [83,84]. Generally speaking, during the past 2 decades, concern has grown about substantial overuse of broad-spectrum antibiotics including not only AMC but also quinolones, second- and third-generation cephalosporins, and second-generation macrolides [85-88].

There is evidence showing the lack of clinically meaningful differences in treatment rates between broad- and narrow-spectrum agents curing acute RTIs [89]. As an example, because many patients with sinusitis improve spontaneously, it has been suggested that narrow-spectrum antibiotics (such as AMX) should be prescribed as first-choices only for very sick patients or for those with a high complications risk. AMX and second- and third-generation cephalosporins should be considered as alternative agents only for the treatment of resistant infections [90,91]. Moreover, despite the absence of consistent supporting data and the risk of promoting drug resistance, some infections are routinely treated with antibiotics even for self-limited illnesses or for those with a predominantly viral aetiology, such as common colds and acute bronchitis [92-94]. Overall, it has been estimated that 55% of all antibiotic prescriptions for RTIs are unnecessary [95,96]. This attitude is unsafe for these patients who are exposed to unjustified risks. It is also critical for the antibiotic itself, which will progressively lose efficacy when used against the strain selected from previous overloaded use.

Choosing the most appropriate antibiotic is difficult, especially in primary care. A variety of factors can affect prescribing behaviour, including the severity of illness, the likelihood of a resistant organism, physician training and local patterns of practice, cost of treatment or formulary restrictions.

The only way to protect these antibiotics, and consequently their efficacy, is to invert the prescription trend. To achieve this goal, several strategies could be adopted to modify physicians’ attitude to prescribing:

- Promote targeted educational intervention strategies towards general physicians, aimed at implementing guidelines for optimising antibiotic prescribing in primary care. There are several examples of successful, tailored interventions in this field, with significant and enduring reductions in prescribing broad-spectrum antibiotics, in favour of those with a narrow spectrum [97,98].
- Involve consumer associations and patients in public education programmes to reduce any inappropriate antibiotic demand and, as a consequence, improper physician prescribing. Particular emphasis should be directed towards the risk of developing resistant strains owing to the widespread and inappropriate use of broad-spectrum antibiotics. It is also important to underline the opportunity to reduce the economic burdens on national health systems, without influencing patients’ proper infection management.
- The growing use of software to support general physicians’ prescription writing is now a reality. Build-up tools to support the correct choice of antibiotics may reduce the level of making inappropriate prescriptions. Such tools may also help to improve prescribers’ counselling before antibiotic treatment. For instance, an automated electronic reminder may activate every time a prescription of AMC is made, to remind prescribers that a period of observation without immediate use of antibiotics may be a valid option for certain conditions, and that the drug should be used cautiously in patients with cholestatic jaundice/hepatic dysfunction, using an alternative antibiotic whenever it is possible.

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Declaration of interest

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