Biomarkers of Antibiotic Toxicity: A Focus on Metronidazole

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Moses W. Bariweni, Vinood B. Patel, Gulrez M. Zariwala, and Raymond I. Ozolua

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M. W. Bariweni (✉)
Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University, Wilberforce Island, Bayelsa State, Nigeria
e-mail: mbariweni@ndu.edu.ng

V. B. Patel · G. M. Zariwala
School of Life Sciences, University of Westminster, London, UK
e-mail: v.b.patel@westminster.ac.uk; m.zariwala@westminster.ac.uk

R. I. Ozolua
Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria
e-mail: ozolua@uniben.edu

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Abstract

Toxicity arising from the use of antibiotics is a limiting factor in health care. Individualized drug therapy has been useful in reducing the occurrence of antibiotic-induced toxicity but it has no quantitative or predictive importance. Biomarker-based strategies can be used to optimize patient-specific response to antibiotic therapy aimed at predicting and reducing antibiotic-induced toxicity. Metronidazole (MTZ), a nitroimidazole drug, is a classical antibiotic with wide application in human and veterinary medicine. Long-term use of MTZ is associated with neurotoxic effects amidst other forms of toxicity. Magnetic resonance imaging (MRI) changes with hyperintensities on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences in the cerebellar dentate nuclei or splenium of the corpus callosum, and genotoxic indices such as sister chromatid exchange (SCE) and mitotic index (MI) in human lymphocytes are biomarkers of MTZ-induced toxicity.

Keywords

Neurotoxicity · Metronidazole · Magnetic resonance imaging · Genotoxicity · Neuropsychiatric · Encephalopathy · Ototoxicity · Cerebellar dysfunction · Sister chromatid exchange · Biomarker · DNA · Hepatotoxicity

Abbreviations

ALT	Alanine aminotransferase
ARG-1	Arginase-1
AST	Aspartate aminotransferase
B2M	Beta-2-microglobulin
CA	Chromosomal aberrations
CPK	Cell proliferation kinetics
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
DSB	Double-strand breakage
ELISA	Enzyme-linked immunosorbent assays
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
GFAP	Glial fibrillary acidic protein
GLDH	Glutamate dehydrogenase
GST-α	Glutathione *S*-transferase
HMGB-1	High-mobility group box-1
IARC	International Agency for Research on Cancer
IGFBP7	Insulin-like growth factor binding protein 7
L-FABP	Liver-type fatty-acid-binding protein
MAP-2	Microtubule-associated protein-2
MBP	Myelin basic protein

MCP-1	Monocyte chemotactic protein-1
MI	Mitotic index
MRI	Magnetic resonance imaging
MTZ	Metronidazole
NGAL	Neutrophil gelatinase-associated lipocalin
OCT	Ornithine carbamoyltransferase
PET	Positron emission tomography
PFOR	Pyruvate: ferredoxin oxidoreductase
PNP	Purine nucleoside phosphorylase
PON-1	Paraoxonase/Arylesterase 1
Rdxa	Nitroreductase
RI	Replication index
SCE	Sister chromatid exchange
SDH	Sorbitol dehydrogenase
T2	Transverse relaxation time
TIMP-2	Tissue inhibitor of metalloproteinases-2
TrxR	Thioredoxin reductase
UCH-L1	Ubiquitin C-terminal hydrolase L1
WHO	World Health Organization

Introduction

Antibiotics are one of the major groups of medicines used for maintenance of health worldwide. Their use has facilitated the treatment of diseases caused by pathogens (Hurkacz et al. 2021). Toxicity is a critical concern facing the use of many classes of antibiotics (Zagaria 2013; Mohsen et al. 2020). Several factors contribute to the occurrence of antibiotic-induced toxicities including indiscriminate use, as well as patient-, drug-, and disease-related factors among many others (Aulin et al. 2021). The concept of individualized drug therapy has been employed to limit the occurrence of drug-induced injury and promote drug safety (De Waele et al. 2014). This concept has greatly reduced the occurrence of antibiotic-induced toxicity, though it is not enough to quantify or foretell the occurrence of toxicity. Understanding human diversity and the interaction of antibiotics with various organs can promote the safe use of antibiotics. The emergence of biomarker-based strategies presents an opportunity to optimize patient-specific response to antibiotic therapy aimed at predicting and reducing antibiotic-induced toxicity (Aulin et al. 2021). However, application of this strategy in clinical practice is still slow as a result of knowledge gaps in terms of drug-patient-disease interaction (Belgrader et al. 1998). Several general organ toxicity biomarkers exist in clinical practice. Identification of patient-linked antibiotic-induced toxicity biomarkers would present a clearer approach to maximize drug therapy with limited toxicity (Griffin et al. 2019). Quantification of antibiotic exposure and changes in toxicity biomarker levels tend to ensure optimum therapeutic outcomes (Aulin et al. 2021).

Overview of Metronidazole

Metronidazole (MTZ) is a nitroimidazole drug developed over six decades ago for the treatment of trichomoniasis (Cosar and Julou 1959). Soon afterward its effectiveness against microaerophilic infections caused by *Giardia lamblia* (Schneider 1961) and *Entamoeba histolytica* (Powell et al. 1966) was demonstrated. MTZ is active against many other anaerobic and microaerophilic bacteria such as *Clostridium spp*. (Freeman et al. 1968; Ahmed et al. 1995; Chin and Hughes 2018), *Fusobacterium fusiforme* (Füzi and Csukás 1969), *Bacteroides fragilis* (Nastro and Finegold 1972), and *Helicobacter pylori* (Hirschl et al. 1988; Kim et al. 2007). MTZ is also effective against *Balantidium coli*, *Campylobacter spp, Gadnerella vaginalis*, and *Desulfovibria spp* (Leitsch 2019). Due to its relatively low cost and availability in oral, intravenous, and topical forms, as well as its rapid antibacterial effectiveness, MTZ is considered to be the gold standard for anaerobic infections, and forms a cornerstone of antibacterial therapy regimens in the WHO essential drug list (Leitsch 2019). MTZ has a wide range of applications in both human and veterinary practice including surgical prophylaxis.

Mode of Action

In contrast to most other antimicrobials, MTZ exhibits pleiotropism in its mode of action and reacts with a large number of molecules (Müller and Gorrell 1983). Importantly, MTZ, which strictly speaking is a prodrug, needs to be reduced at its nitro-radical group in order to become toxic to susceptible organisms (Edwards 1993). Several nitro-intermediates including oxamic acid and acetamide are generated during its metabolism; however, the cytotoxic intermediates are yet to be identified as they are rather unstable (Church et al. 1988; Dingsdag and Hunter 2018; Leitsch 2019) and the formation of these two derivatives does not account for all nitrogen atoms in the parent molecule. Reduction of MTZ takes place under anaerobic or microaerophillic conditions involving both enzymatic and non-enzymatic pathways (Willson and Searle 1975; Leitsch et al. 2009, 2011). There are distinct states of reduction involving electron transfer to the nitro group including the nitro-radical anionic state (transfer of one electron) (Lindmark and Müller 1976; Edwards 1993; Kulda 1999), the two-electron (nitroso) and the four-electron (nitroxyl) states (Wardman 1985).

In general, the first step in the mechanism is the reduction of the nitro group of the drug to the corresponding nitro-anion radical, other processes include redox recycling, formation of reactive radical species, and formation of nitroso, hydronitroxide, and amine compounds (Reveles et al. 2014; Lessa et al. 2015; Ceruelos et al. 2019). Several enzymes suggested to be involved in the reductive activation of MTZ include the pyruvate: ferredoxin oxidoreductase (PFOR) which catalyzes electron transfer via its iron-sulfur clusters resulting in the generation of nitro-radical anion (Lindmark and Müller 1976; Moreno et al. 1984; Chapman et al. 1985). Other enzymes thought to generate nitro-radical anions in vitro include the

cytochrome *P-450* reductase, xanthine oxidase, aldehyde oxidase, and ascorbate (Moreno et al. 1984; Ramakrishna and Ronald 1987). The nitro-anions thus produced can be further reduced under hypoxic conditions to form their corresponding nitroso, hydronitroxide, and amine compounds (Ramakrishna and Ronald 1987). Several flavin-dependent enzymes including thioredoxin reductase (TrxR) (Leitsch et al. 2007, 2009) and nitroreductase (Rdxa) (Olekhnovich et al. 2009) have also been described in the reduction of MTZ. The nitro-derivatives produced from the reduction of MTZ form thiol adducts which react with nucleotides (Ludlum et al. 1988) and cysteine (Leitsch et al. 2007), giving rise to GC-CG transversions leading to single and double DNA strand breaks, especially in AT clusters (Talapatra et al. 2010; Ceruelos et al. 2019). Degradation of translation elongation factor 1-γ (Leitsch et al. 2012) has also been described for the reductive derivatives of MTZ, all these effects put together may be responsible for its cytotoxicity.

Pharmacokinetics and Toxicity

MTZ is orally active with almost complete absorption and over 90% bioavailability; absorption is unaffected by infection (Ralph et al. 1974). Rectal and intravaginal absorption are 67–82%, and 20–56%, of the dose, respectively (Bergan et al. 1984). MTZ is distributed widely and has low protein binding (<20%) with the volume of distribution at steady state in adults ranging between 0.51 and 1.1 L/kg (Gulaid et al. 1978; Houghton et al. 1979). MTZ reaches 60–100% of plasma concentrations in most tissues studied, including the central nervous system, but does not reach high concentrations in placental tissue (Mattila et al. 1983). Clinical concentrations of MTZ seen in human plasma after a 2 g, one-time oral dose, commonly used to treat *T. vaginalis,* are approximately 300 μM; whereas peak concentrations of MTZ reached in human plasma after twice daily dosing with 500 mg (e.g., regimens to treat bacterial vaginosis) do not exceed 100 μM (Wang et al. 2011). MTZ is extensively metabolized by the liver to several metabolites. The hydroxy metabolite has biological activity of 30–65% and a longer elimination half-life than the parent compound (Somogyi et al. 1983). The majority of MTZ and its metabolites are excreted in urine and feces, with less than 12% excreted unchanged in urine (Gulaid et al. 1978; Houghton et al. 1979; Somogyi et al. 1983). The pharmacokinetics of MTZ is affected by acute or chronic renal failure, hemodialysis, continuous ambulatory peritoneal dialysis, age, pregnancy, or enteric disease (Somogyi et al. 1983; Houghton et al. 1985).

Although MTZ is generally well tolerated, its adverse effects are predominantly mild gastrointestinal disturbances such as nausea, abdominal pain, and diarrhea (Chin and Hughes 2018). Several neuropsychiatric effects (encephalopathy, cerebellar dysfunction, and seizures) as well as other side effects such as vertigo, impaired sleep, dizziness, and states of confusion, excitation, and depression (Ahmed et al. 1995) have been reported when the drug is used between 1 week and 12 weeks at doses ranging between 1 g and 2 g per day in humans and 40 mg/kg in animals (Kim et al. 2007). Apart from neurotoxicities, other adverse effects of

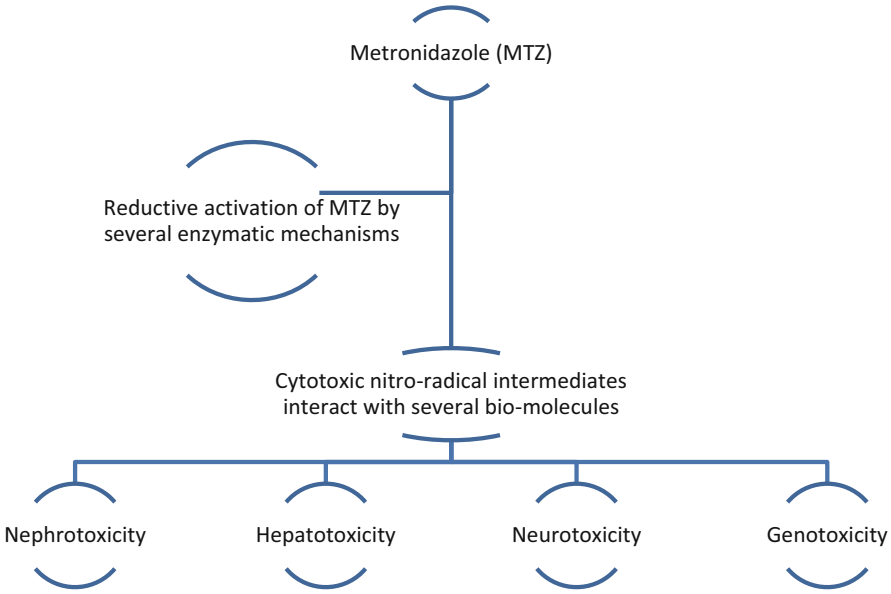

Fig. 1 Schematic representation of MTZ-induced toxicity

MTZ have been reported. These include DNA damage in human lymphocytes (Roe 1983; Celik and Ates 2006), bone marrow suppression (El-Nahas and El-Ashmawy 2004), immunosuppression in human blood lymphocytes (Mohammad et al. 2008), few reported cases of ototoxicity (O'Donnell and Barker 2016), and delayed immune-allergic hepatocellular liver injury (Kancherla et al. 2013). MTZ-induced toxicity seems to be due to the intermediates produced during its metabolism (Fig. 1) as it is a prodrug itself.

Biomarkers of Antibiotic-Induced Toxicity

Antibiotic-induced toxicities have become a major concern affecting different classes of medicines in the treatment of infectious diseases (Zagaria 2013) and these toxicities occur via various mechanisms (Fig. 2). These antibiotic-induced toxicities can present on short-term or long-term basis. The acute toxic effects of antibiotics are often reversible on discontinuation of the offending agent. However, they may result in treatment failure owing to abrupt discontinuation of therapy and this contributes to antibiotic resistance. Long-term toxicities often result in permanent damage and are often detected after chronic administration of the offending agent (Aulin et al. 2021), howbeit some long-term effects manifest early in the course of treatment. Quantification of antibiotic-induced toxicity is mostly not feasible in patients as it relies basically on histological findings which are sometimes postmortem.

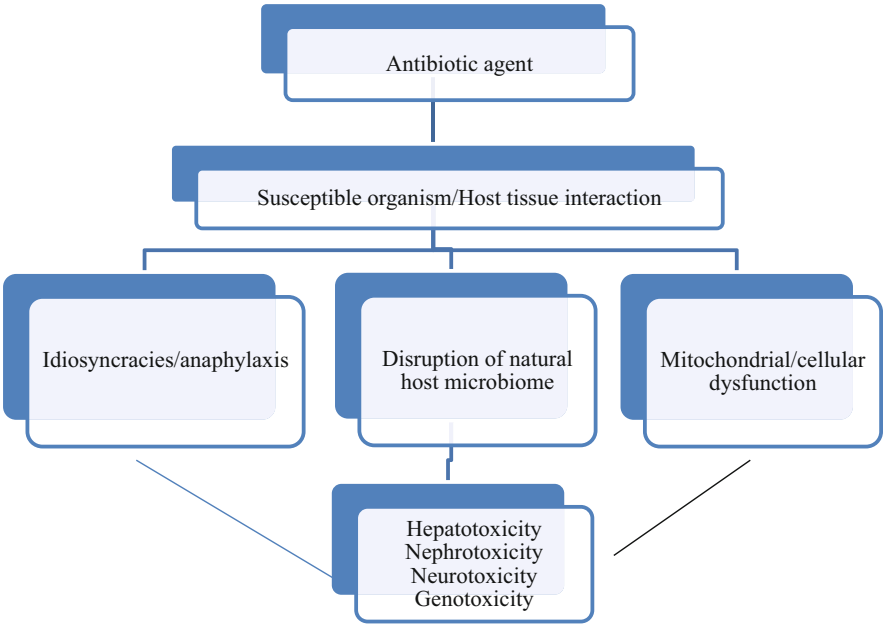

Fig. 2 Mechanisms of antibiotic-induced toxicities

Antibiotic-induced toxicity biomarkers can be useful in both quantification and prediction of toxicity.

Several biomarkers are available in clinical practice for accessing organ function. Prediction of antibiotic-induced toxicity may require specialized biomarkers as the general biomarkers are insufficiently specific and sensitive (Tajima et al. 2019). Biomarkers may be classified as predictive or prognostic (Atkinson et al. 2001; De Gruttola et al. 2001). Predictive biomarkers are useful tools in stratification of patients with tendency to develop antibiotic-induced toxicity on the premise of biomarker availability or absence. The availability of a specific toxicity biomarker in a patient can be used to single out high-risk patients and hence avoid toxicity as sensitivity and specificity are strictly adhered to (Dupuy et al. 2013). Biomarkers which can identify early signs of toxicity are invaluable in optimizing antibiotic therapy allowing for dosage adjustment where necessary (Tajima et al. 2019). A major setback in the use of biomarkers to maximize antibiotic therapy is the disparity in their measurement, interpretation, and translation of data which are mainly obtained from animal studies to humans.

Biomarkers of Nephrotoxicity

Nephrotoxicity is associated with a number of antibiotics. There are several traditional biomarkers of kidney function, such as serum creatinine and blood

urea nitrogen which lack specificity and sensitivity; these traditional markers are late indicators of kidney toxicity as they often rise after some loss of kidney function (Bonventre et al. 2010). A number of blood and urinary biomarkers including beta-2-microglobulin (B2M) produced by activated lymphocytes (Gautier et al. 2014); kidney injury molecule-1 (KIM-1), an epithelial cell adhesion molecule found in the proximal tubules, monocyte chemotactic protein-1 (MCP-1), and cystatin C, a component of all nucleated cells, have been identified as biomarkers for early antibiotic-induced kidney damage (Ozer et al. 2010; Vaidya et al. 2010). Neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty-acid-binding protein (L-FABP) are emerging early nephrotoxicity biomarkers (Table 1) requiring further human studies (Griffin et al. 2019). Clusterin, a glycosylated protein commonly found in the kidney, is also an early nephrotoxicity marker secreted in urine, although there is a paucity of information regarding its usefulness in human studies (Rosenberg and Silkensen 1995). Out of these nephrotoxicity biomarkers, KIM-1, B2M, clusterin, and cystatin C are accepted by the Food and Drug Administration (FDA) and European Medicines Agency (EMEA) as highly sensitive and specific urinary biomarkers (Griffin et al. 2019). There is ongoing research to finding more specific and sensitive nephrotoxicity biomarkers with universal acceptability. Some promising molecules include interleukin-18 that demonstrates urinary increase at least a day before increase in serum creatinine levels (Edelstein 2017) and insulin-like growth factor binding protein 7 (IGFBP7), a marker of apoptosis in combination with tissue inhibitor of metalloproteinases-2 (TIMP-2), which are also recognized by the FDA howbeit with limited applicability (Vijayan et al. 2016).

Various antibiotics have negative effects on the kidneys, the aminoglycosides and polymyxins have known nephrotoxic effects. So far there are few reports of nephrotoxicity in animals linked to MTZ (Somogyi et al. 1983) with no reports from human data, although the histological results do not conform with the biomarker data from these studies. In summary, there are no specific biomarkers of MTZ-induced nephrotoxicity as there is a paucity of information in that regard.

Table 1 Markers of antibiotic-induced kidney toxicity

Regular markers	Predictive/Emerging biomarkers
Total protein	Beta-2-microglobulin (B2M)
Bilirubin	Kidney injury molecule-1 (KIM-1)
Creatinine	Monocyte chemotactic protein-1 (MCP-1)
Blood urea/Nitrogen	Cystatin C
Albumin	Neutrophil gelatinase-associated lipocalin (NGAL)
Kidney biopsy	Liver-type fatty-acid-binding protein (L-FABP)
CT scan	Clusterin
	Interleukin-18
	Insulin-like growth factor binding protein 7 (IGFBP7)
	Tissue inhibitor of metalloproteinases-2 (TIMP-2)

Hepatotoxicity Biomarkers

Hepatotoxicity is a major concern in therapeutics. Several classes of antibiotics are known to cause antibiotic-induced liver damage which may sometimes be fatal or result in severe hepatic damage. The liver enzymes (alanine [ALT] and aspartate [AST] aminotransferases) are traditional markers of liver injury, they lack the specificity and sensitivity required of predictive biomarkers of antibiotic-induced toxicity (Campion et al. 2013). Other factors like diet, exercise, and disease condition affect their serum concentrations. Changes in their serum concentrations also occur after some damage has occurred in the liver and sometimes these changes may not correlate with the histology of the liver (Bonventre et al. 2010). Glutamate dehydrogenase (GLDH), high-mobility group box 1 (HMGB-1), keratin-18 (k18), microRNA-122, and ornithine carbamoyltransferase (OCT) are more sensitive markers of hepatotoxicity compared to the traditional markers (Table 2) including the blood levels of aminotransferases and total bilirubin (O'Brien et al. 2002; Campion et al. 2013). Other markers of hepatic damage include paraoxonase/arylesterase 1 (PON-1), purine nucleoside phosphorylase (PNP), arginase 1 (ARG-1), sorbitol dehydrogenase (SDH), and glutathione *S*-transferase (GST-α). In addition, current research in proteomic technologies may lead to discovery of more sensitive biomarkers.

MTZ is not a known hepatotoxicant despite being extensively metabolized by the liver CYP2A6. Animal studies show variable reports with some changes in liver enzymes without histocompatibility. Most effects of MTZ on the liver are mild and reversible on withdrawal of the drug. Data from animal studies mostly do not translate to human effects although a few reports of MTZ-induced hepatotoxicity do exist (Kancherla et al. 2013). Despite the fact that antibiotic-induced hepatic damage occurs from use of several classes of antibiotics with amoxicillin-clavulanate combination being the most reported (Chalasani et al. 2008), it is scarcely so for MTZ. Antibiotic-induced liver damage due to delayed idiosyncratic reactions is rare with complex causes including drug and host (genetic and non-genetic) factors. It is challenging to investigate because of its rarity, the lack of experimental models, the number of medications that might cause it, and challenges to diagnosis. There is currently no biomarker for MTZ-induced hepatotoxicity.

Table 2 List of antibiotic-induced hepatotoxicity markers

Traditional markers	Predictive/Emerging biomarkers
Alanine aminotransferase (ALT)	Glutamate dehydrogenase (GLDH)
Aspartate aminotransferase (AST)	High-mobility group box 1 (HMGB-1)
Alkaline phosphatase (ALP)	Keratin-18 (k18)
Albumin	MicroRNA-122
Protein	Ornithine carbamoyltransferase (OCT)
Gamma-glutamyltransferase	Paraoxonase/Arylesterase 1 (PON-1)
Lactate dehydrogenase	Purine nucleoside phosphorylase (PNP) Arginase (ARG-1)
Prothrombin time	Sorbitol dehydrogenase (SDH)
	Glutathione *S*-transferase (GST-α)

Neurotoxicity Biomarkers

Neurotoxicity has been linked to a number of common antibiotics but diagnosis and prediction is a major challenge. Traditional means of identifying neurotoxicity involves the use of complex functional assessments, such as behavioral changes and electrophysiological measures, including histopathological assessment of neural tissues by the hematoxylin/eosin staining methods (Bolon et al. 2013). These methods lack the sensitivity and specificity expected from biomarkers. Biological fluid–based markers and emerging imaging technologies (Table 3) from minimally invasive techniques can help diagnose and predict neurotoxicity with wide applicability that is relevant across animal models and can be translated to clinical data. Some biofluid-based markers of neurotoxicity include microRNAs, F2-isoprostanes, translocator protein, glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase L1 (UCH L1), myelin basic protein (MBP), microtubule-associated protein-2 (MAP-2), and total tau (Roberts et al. 2015). Enzyme-linked immunosorbent assays (ELISA) are already available for most of these biomarkers although they are not specific for antibiotic-induced neurotoxicity as same markers are present in most neurodegenerative and neuropsychiatric conditions (Rosen and Zetterberg 2013). A major setback is that acquisition of some of these biomarkers such as those in cerebrospinal fluid (CSF) requires invasive sampling. Neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) also serve as biomarkers and have the advantage of being minimally invasive compared to biomarkers from the CSF (Hanig et al. 2014). A combination of imaging techniques and fluid-based markers would provide both diagnostic and predictive biomarkers of antibiotic-induced neurotoxicity.

The most worrisome adverse effect of MTZ is neurotoxicity which includes both central and peripheral neurotoxicities. MRI is the mainstay of predicting and diagnosing MTZ-induced neurotoxicities. This technique can predict cellular toxicity as it detects alterations in tissue characteristics such as cellular integrity, cell density, and water redistribution in vivo (Roberts et al. 2015). The most useful MRI technique measures T2 relaxation since it is simple and can provide evenly distributed

Table 3 List of traditional and predictive biomarkers of antibiotic-induced neurotoxicity

Traditional markers	Predictive biomarkers	MTZ toxicity biomarkers
Motor activity tests Behavioral tests Electroencephalogram Nerve conduction velocity	microRNAs F2-isoprostanes Translocator protein Glial fibrillary acidic protein (GFAP) Ubiquitin C-terminal hydrolase L1 (UCH L1) Myelin basic protein (MBP) Microtubule-associated protein-2 (MAP-2) Total tau	Magnetic resonance imaging T2-weighted and fluid-attenuated inversion recovery (FLAIR) hyperintensities

Table 4 Antibiotic-induced genotoxicity markers

Traditional markers	Emerging biomarkers	MTZ toxicity biomarkers
Comet assay Bacterial Ames test Alkaline unwinding Hydroxyapatite chromatography	Replication index (RI) Micronuclei (MN) Chromosomal aberrations (CA) DNA strand breaks (DSB)	Sister chromatid exchanges (SCEs) Mitotic index (MI)

time course scans and quantitative metrics (Hanig et al. 2014). The biomarkers of MTZ-induced neurotoxicity are typical bilateral or symmetrical imaging changes with hyperintensities on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences in the cerebellar dentate nuclei or splenium of the corpus callosum (Kim et al. 2007; Sørensen et al. 2020), being the most affected regions consistent with all MTZ-induced neurotoxic events.

Genotoxicity Biomarkers

Long-term use of antibiotics with genotoxic effects may cause mutations and consequently cancers but from clinical data most antibiotics with genotoxic effects in animal studies are not carcinogenic in humans. MTZ is thought to exert its antibacterial effect by causing DNA damage in susceptible organisms (Talapatra et al. 2010; Ceruelos et al. 2019), and genotoxicity in human lymphocytes has been reported as one of its adverse effects (Roe 1983; Celik and Ates 2006). MTZ is reported to alter the frequency of SCEs in peripheral blood lymphocytes and MI of the black-stripped capuchin (Mudrya et al. 2011). However, mutagenicity and carcinogenicity of MTZ in humans is a matter of current debate as many conflicting reports exist in literature (Konopacka et al. 1990; Buschini et al. 2009; Mudrya et al. 2011), most of which are animal data with a few on human lymphocytes (Roe 1983; Celik and Ates 2006). Even with these conflicting data the International Agency for Research on Cancer (IARC) classifies it as carcinogenic (Brambilla et al. 2012). Traditional methods of identifying genotoxicity (Table 4) are available but they are devoid of predictive capacity. Some biomarkers of antibiotic-induced genotoxicity include mitotic index (MI), cell proliferation kinetics (CPK) measured as replication index (RI), sister chromatid exchanges (SCEs), micronuclei (MN), chromosomal aberrations (CA), and DNA strand breaks (DSBs) (Mudrya et al. 2011). The most reported biomarker of MTZ-induced genotoxicity is SCE and reduced MI in human lymphocytes.

Application to Prognosis

MTZ is a widely used antibiotic with clinical efficacy across all age groups and gender. So far toxicities have been reported in adults and some geriatric patients (Chin and Hughes 2018). No organ toxicity has been reported in children apart from

the regular side effects, although it could be due to underreporting. The biomarkers identified for MTZ-induced toxicities could be studied and applied safely in children receiving long-term treatment with MTZ as MRI scans are devoid of X-rays (Zhang et al. 2019; Zagaria 2013).

Mini-Dictionary of Terms

- **Genotoxicity**: alteration of DNA or other genetic materials by a toxicant.
- **Hepatotoxicant**: a substance which when introduced into the body has the potential to harm the liver.
- **Invasive sampling**: collection of biological samples requiring puncturing of skin or other tissues with medical equipment.
- **Microaerophilic**: conditions requiring minute quantities of free oxygen.
- **Pleiotropism**: a phenomenon in which an active drug molecule has multiple mechanisms of action by interacting with several biological molecules.

Key Facts of Antibiotic-Induced Toxicity

- Long-term high-dose use of antibiotics can result in organ damage which may be irreversible.
- Individualized therapy or therapeutic drug monitoring is key in reducing antibiotic-induced toxicity.
- Individualized therapy is not sensitive enough to predict or prevent antibiotic-induced toxicities.
- Identification and incorporation of biomarker-based treatment guidelines into clinical practice are key to predicting, quantifying, and preventing antibiotic-induced toxicity.
- A knowledge gap exists between the availability and functionality of biomarkers from animal studies and their application in humans.

Summary Points

- Antibiotic-induced toxicities are largely unquantified and insufficiently reported.
- Fluid-based biological molecules can predict and diagnose persons prone to antibiotic-induced toxicity.
- The toxic effects of MTZ are mainly due to the formation of toxic anionic intermediates.
- Neurotoxicities and probably genotoxicity are the most prominent MTZ-induced toxicities.
- A combination of MRI and fluid-based biological molecules are the best biomarkers of MTZ-induced toxicity.

Conclusion

Toxicity is a serious complication and limiting factor to maximizing antibiotic therapy. Institution and incorporation of biomarker-based treatment guidelines in clinical practice will go a long way in mitigating organ injury due to antibiotic use. A key factor that will aid this process is the harmonization of baseline data originating from the large number of biomarkers already in existence, as well as their interpretation and translation into clinical practice. Several biomarkers may need to be combined to give definitive prediction or diagnosis of antibiotic-induced toxicity. Further multisectorial research is required to bridge the knowledge gap that exists and also create easy-to-use cost-effective test kits to achieve the desired goal.

Cross-References

- ▶ Biomarkers of Neurotoxicity
- ▶ DNA Adducts as Biomarkers in Toxicology
- ▶ Drug-Induced Nephrotoxicity and Use of Biomarkers

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