

LETTERS

Comparison of the in vitro susceptibility of rifaximin versus norfloxacin against multidrug resistant bacteria in a hospital setting. A proof-of-concept study for use in advanced cirrhosis

We read with interest the recent letter to the editor from Waidmann *et al*¹ investigating the effect of multidrug resistant (MDR) bacteria intestinal colonisation on the prognosis of patients with cirrhosis. The authors concluded that infections due to MDR bacteria and asymptomatic intestinal colonisation with MDR bacteria are a risk factor for mortality in cirrhosis. That information expands the relevance of preventing and treating infections due to MDR bacteria in patients with cirrhosis.

Infections due to MDR bacteria are mostly nosocomial in origin and represent an increasing threat in decompensated cirrhosis, due to the high requirement of changing antibiotics and its associated mortality.² According to the actual pathogenic hypothesis of spontaneous infections in cirrhosis, a nosocomial spontaneous infection due to MDR bacteria should be preceded by its colonisation of the intestinal lumen and further translocation. Therefore primary prophylaxis with the adequate drug might reduce its incidence. Norfloxacin (NOR) is a poorly absorbable quinolone that is widely used as primary and secondary prophylaxis of infections in

advanced cirrhosis, decreasing the incidence of bacterial infections, and of hepatorenal syndrome and increasing survival. However, recently, its use has been shown to be an independent predictive factor for the development of infections due to MDR bacteria.³ Therefore, alternatives to NOR are needed in this setting.

Rifaximin (RFX) is a broad-spectrum antibiotic of the ansamicins family that is not absorbed from the GI tract and reaches high levels in the intestinal lumen. It rarely induces bacterial resistances and its effects disappear rapidly after finishing administration.⁴ Its usefulness has been proved in patients with advanced cirrhosis and hepatic encephalopathy.³ In this investigation we aimed to compare the in vitro bactericidal activity of NOR and RFX against a large series of MDR bacteria that are detailed in table 1.

MDR bacteria are strains resistant to at least three of the main antibiotic families, including β -lactams. Bacteria here investigated were isolated from different specimens (colonisation or infection) obtained from patients admitted to the Hospital General Universitario de Alicante, Spain, from January to May 2013. The micro-organisms were identified by MALDI-TOF (BRUKER, F Soria, Spain) methods and initially susceptibility test was performed by Microscan (WalkAway 96 Plus, Siemens, Health Care Diagnostics, S L, Germany), and afterwards the full range of minimal inhibitory concentrations (MICs) of RFX and NOR were determined by an agar dilution method following the guidelines of the Clinical and Laboratory Standards Institute.⁴

RFX and NOR MIC₅₀ and MIC₉₀ obtained for the tested bacteria are shown in table 1. As detailed, MIC₉₀ for RFX was lower than that for NOR in all cases but for susceptible *Escherichia coli*, and *Citrobacter*, *Morganella* and *Enterobacter* MDR (equally effective as NOR). These MIC₉₀ are easily achieved due to the high concentration of RFX in the intestinal lumen following its oral administration.

Information here provided demonstrates that RFX shows bactericidal activity against a large series of MDR bacteria collected from different patients in a tertiary hospital setting and in the vast majority of cases it is significantly higher than that observed with NOR. Therefore information in vitro suggests that RFX may be considered as an alternative to NOR, either as a primary or a secondary prophylaxis of bacterial infections caused by MDR bacteria in hospitalised patients with advanced cirrhosis. However this hypothesis should be confirmed through the design of an appropriate clinical trial.

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Table 1 Minimal inhibitory concentration (MIC) ($\mu\text{g/mL}$) and range of rifaximin and norfloxacin for susceptible and resistant bacteria

Micro-organisms	Number of isolates	Rifaximin			Norfloxacin		
		MIC ₅₀ , $\mu\text{g/mL}$	MIC ₉₀ , $\mu\text{g/mL}$	MIC range, $\mu\text{g/mL}$	MIC ₅₀ , $\mu\text{g/mL}$	MIC ₉₀ , $\mu\text{g/mL}$	MIC range, $\mu\text{g/mL}$
MS <i>S. epidermidis</i>	10	≤ 0.007	≤ 0.007	≤ 0.007 –8	0.25	64	0.015–64
MR <i>S. epidermidis</i>	20	≤ 0.007	≤ 0.007	≤ 0.007 –16	2	32	0.015–32
MS <i>S. aureus</i>	20	≤ 0.007	≤ 0.007	≤ 0.007	1	128	0.5–128
MR <i>S. aureus</i>	20	≤ 0.007	0.06	≤ 0.007 –2	128	>128	32–>128
PS <i>E. faecalis</i>	20	2	4	0.25–4	4	64	2–>128
PR <i>E. faecium</i>	16	4	16	1–>128	>128	>128	16–>128
<i>Escherichia coli</i> susceptible	20	8	8	1–16	0.125	1	0.03–1
MDR <i>E. coli</i>	23	8	16	4–16	64	128	2–>128
MDR <i>Kebsiella pneumoniae</i>	27	32	64	16–128	32	128	0.06–>128
MDR <i>Proteus mirabilis</i>	5	4	4	0.06–4	8	64	0.05–64
MDR <i>Citrobacter</i> , <i>Morganella</i> and <i>Enterobacter</i>	5	16	32	0.03–32	0.25	32	0.125–32
MDR <i>P. aeruginosa</i>	13	16	16	8–16	16	128	0.125–128
MDR <i>A. baumannii</i>	14	1	4	0.25–4	>128	>128	128–>128

MDR, multidrug-resistant; MS, methicillin-susceptible; MR, methicillin-resistant; PS, penicillin-susceptible; PR, penicillin-resistant.

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