

Safety of fluconazole in paediatrics: a systematic review

Oluwaseun Egunsola · Abiodun Adefurin ·
Apostolos Fakis · Evelyne Jacqz-Aigrain ·
Imti Choonara · Helen Sammons

Received: 9 July 2012 / Accepted: 27 November 2012 / Published online: 17 January 2013
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Abstract

Purpose To determine the safety of fluconazole in neonates and other paediatric age groups by identifying adverse events (AEs) and drug interactions associated with treatment.

Methods A search of EMBASE (1950–January 2012), MEDLINE (1946–January 2012), the Cochrane database for systematic reviews and the Cumulative Index to Nursing and Allied Health Literature (1982–2012) for any clinical study about fluconazole use that involved at least one paediatric patient (≤ 17 years) was performed. Only articles with sufficient quality of safety reporting after patients' exposure to fluconazole were included.

Results We identified 90 articles, reporting on 4,209 patients, which met our inclusion criteria. In total, 794 AEs from 35 studies were recorded, with hepatotoxicity accounting for 378 (47.6 %) of all AEs. When fluconazole was compared with placebo and other antifungals, the relative risk (RR) of hepatotoxicity was not statistically different [RR 1.36, 95 % confidence interval (CI) 0.87–2.14, $P=0.175$ and RR 1.43, 95 % CI 0.67–3.03,

$P=0.352$, respectively]. Complete resolution of hepatotoxicity was achieved by 84 % of patients with follow-up available. There was no statistical difference in the risk of gastrointestinal events of fluconazole compared with placebo and other antifungals (RR 0.81, 95 % CI 0.12–5.60, $P=0.831$ and RR 1.23, 95 % CI 0.87–1.71, $P=0.235$, respectively). There were 41 drug withdrawals, 17 (42 %) of which were due to elevated liver enzymes. Five reports of drug interactions occurred in children.

Conclusion Fluconazole is relatively safe for paediatric patients. Hepatotoxicity and gastrointestinal toxicity are the most common adverse events. It is important to be aware that drug interactions with fluconazole can result in significant toxicity.

Keywords Fluconazole · Safety · Neonates · Paediatrics · Hepatotoxicity

Background

Invasive candidiasis is associated with high morbidity and mortality in neonates and children, with the highest incidence in premature neonates. Studies in neonates have shown an incidence rate of 2–28 % depending on birth weight [1]. Amphotericin B is the drug of choice for the treatment of invasive candidiasis; however, nephrotoxicity has been associated with this drug [2]. Fluconazole remains a suitable alternative and has also been used routinely as prophylaxis for very low birth weight neonates and children with other risk factors. Risk factors in neonates include prematurity, broad spectrum antibiotics, central venous catheter, mechanical ventilation, use of H₂ receptor antagonists and parenteral nutrition. Immunosuppression from endogenous or exogenous causes, such as cystic fibrosis, malignancy, drug therapy (cytotoxics, corticosteroids, immunosuppressives),

O. Egunsola (✉) · A. Adefurin · I. Choonara · H. Sammons
Academic Division of Child Health, Derbyshire Children's
Hospital, University of Nottingham, Derby DE22 3DT, UK
e-mail: oluwaseun.egunsola@nottingham.ac.uk

A. Fakis
Department of Research & Development, Royal Derby Hospital,
Derby, UK

E. Jacqz-Aigrain
Department of Paediatric Pharmacology and Pharmacogenetics,
University of Paris Diderot, Sorbonne Paris Cité,
INSERM CIC 9202,
Paris, France

E. Jacqz-Aigrain
Department of Paediatric Pharmacology and Pharmacogenetics,
Hôpital Robert Debré, 75019 Paris, France

haematological diseases, organ or bone marrow transplantation and prolonged intensive care, are factors in paediatric patients beyond the neonatal period [3, 4].

Fluconazole, a bis-triazole broad spectrum antifungal agent discovered by Richardson et al. during a programme initiated by Pfizer Central Research in 1978 [5], is a suitable alternative to amphotericin B. It is available as an oral tablet, oral suspension and intravenous formulation. Its antifungal activity is achieved by preventing fungal membrane sterol synthesis through the inhibition of cytochrome P450 (CYP)-dependent lanosterol C-14 α -demethylase conversion of lanosterol to ergosterol, resulting in an impairment of fungal cell replication. Although CYP is also present in mammalian cells, fluconazole is highly selective for fungal CYP [6, 7].

Fluconazole is well absorbed orally with extensive bioavailability, and most of the drug is excreted unchanged in the urine; only 11 % is excreted as metabolites, while a small percentage is excreted in the faeces. The elimination half-life of the drug is about 30 h (range 20–50 h), with a faster rate of elimination in older children than adults. In neonates, however, the mean plasma elimination half-life is longer (55–90 h) [8–10].

Fluconazole is licensed in children for mucosal candidiasis, invasive candidiasis and prophylaxis against candidal infections in immunocompromised patients. Common adverse reactions ascribed to the drug from clinical trials include deranged liver enzymes, cholestasis, headache, skin rash and gastrointestinal symptoms [11].

Due to the increasing use of the drug as prophylaxis and for the treatment of fungal infections in paediatric and neonatal patients, as well the need to identify toxicity associated with treatment, we decided to undertake a systematic review of safety data published on fluconazole in these populations.

Method

Search strategy

We searched MEDLINE (1946–January 2012), EMBASE (1950–January 2012), the Cochrane database for systematic reviews, Cumulative Index to Nursing and Allied Health Literature (CINAHL1982–January 2012) and the Cochrane library (Cochrane Central Register of Controlled Trials, Cochrane database of systematic reviews, and Database of abstracts of reviews of effects) for any clinical study about fluconazole use that involved at least one paediatric patient (≤ 17 years). Any study with involvement of a paediatric age group participant taking at least a single dose of fluconazole was eligible. Only studies with a report of safety after exposure to fluconazole in the paediatric patients were included. There was no restriction on the language of

publication of the articles as translations to extract relevant data were done; where translations were not possible, abstracts containing relevant data were used. Also included in this review were any clinical study, whether comparative or non-comparative, randomised controlled trials (RCTs) or case reports and also letters to the editors that documented exposure of a paediatric patient to fluconazole and reported on safety. Included articles and extracted data were validated by two reviewers. Search terms comprised free text words and subject headings. These included terms relating to azole or imidazole or fluconazole, adverse effects or adverse drug reactions or side effects, pharmacokinetics and drug interactions.

Data extraction

Data extracted from each study included the year of publication, type of study, number of paediatric patients exposed, age of paediatric patients exposed, doses of fluconazole used, route of administration and safety data. The safety data extracted were occurrence of any adverse event (AE), any drug interactions, any withdrawal due to AEs and any drug-related death.

Data quality assessment

To minimise the risk of bias, we assessed the quality of included RCTs using the CONSORT checklist for reporting of harm [12]. All RCTs with scores of ≥ 6 out of nine criteria were considered to provide good quality safety reporting. Cohort studies were scored using the STROBE checklist [13], where a score of >70 % is considered to be good. Case series were evaluated using the health technology assessment checklist [14], and all studies fulfilling the good or satisfactory criteria were included.

Data collection

The relevant data were extracted onto the data extraction form. Participants in the study were grouped into paediatric age groups of preterm neonates (<36 weeks gestation, 0–27 days), full-term neonates (0–27 days, >37 weeks gestation), infants and toddlers (28 days–23 months), children (2–11 years) and adolescents (12–17 years). All reported AEs were pooled together from the various studies. The duration of treatment was grouped into <21 , 21–42 and >42 days; the treatment dose was grouped into <3 , 3–6 and >6 mg/kg; the route of administration was recorded as intravenous (IV), oral or IV and oral.

Statistical analysis

Meta-analysis was performed using the Stata/IC v.11 statistical package (StataCorp LP, College Station, TX). Only

those studies rated as good were included in the meta-analysis. Studies with zero frequency were included in the meta-analysis by entering 0.5 to zero cells so that all of the information could be used.

The relative risk (RR) was calculated for these binary outcomes (RR >1 indicates a positive effect of fluconazole). We calculated the pooled relative risks with fixed effect models using the Mantel and Haenszel method. The heterogeneity of the model was examined by calculating the DerSimonian and Laird's Q statistic [15] and the I²-statistic [16]. Both were compared with a chi-square distribution with degrees of freedom (df) equal to the number of trials minus one. We used the Q statistic for testing the presence of heterogeneity and the I²-statistic for estimating the degree of heterogeneity. When heterogeneity was observed, we used the with random effect models as suggested by DerSimonian and Laird [15].

The forest plots have been created for presenting the pooled effects of fluconazole. The effects of indication, age groups, dose range, route of administration and duration of treatment on risk of AEs in the fluconazole groups against the active comparator were assessed using random effect models.

Poisson regression analysis was used to test the effect of indication, age groups, dose groups, route of administration and duration of treatment on incidence of AEs and hepatotoxicity in the fluconazole group. The incidence–rate ratios (IRR) are reported from the Poisson regression analysis. All results are reported with 95 % confidence intervals (CIs), and all *P* values are two-tailed.

Results

Our search revealed 1,702 articles, of which 117 met our inclusion criteria (Fig. 1). These were reduced to 90 following assessment of data quality. Two articles in foreign languages (Chinese and Hebrew) were excluded because the articles could not be translated. All 90 articles were published between 1986 and 2011, and the most frequent type of studies was the case report, followed by the case series and the RCT (Table 1). Thirty-one (34 %) of the studies involved neonates only.

The largest group of patients who received fluconazole were taking part in RCTs (1,793 patients). These studies compared fluconazole with griseofulvin, placebo, nystatin, amphotericin B and other azole antifungals. One study compared different routes of administration [17]. Seven of the 14 RCTs were exclusively conducted in neonates (term and preterm) [17–23], while the remainder involved children across the paediatric age spectrum (birth–17 years) [24–31]. Fluconazole was used as prophylaxis in six of the eight neonatal RCTs.

The second largest group of patients on fluconazole (1,564) were enrolled in cohort studies [32–38]. All cohort study patients were preterm neonates, with fluconazole administered either prophylactically orally or intravenously. The other large group of patients (795) were in case series [39–59]. Fifteen of these studies were conducted in term and preterm neonates, while the others cut across the paediatric age group. Seventy-seven patients were involved in eight pharmacokinetic studies [60–67], three of which were performed exclusively in preterm and term neonates.

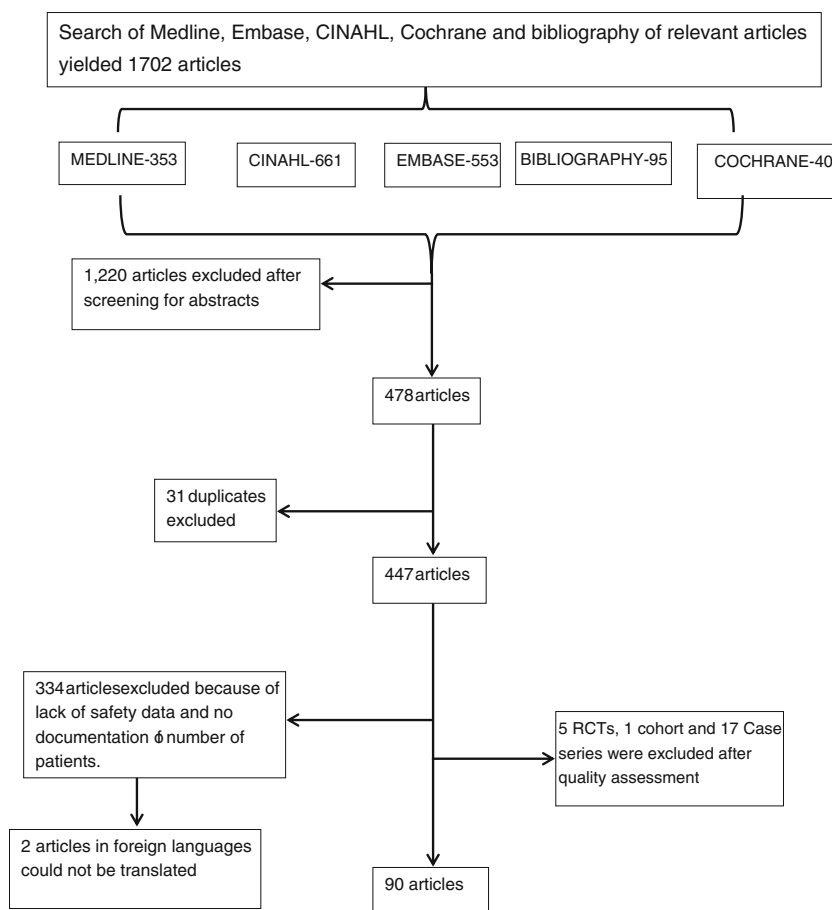
Dosage and administration

Fluconazole was either administered as prophylaxis or therapeutically. The median prophylactic dose was 3 mg/kg/day [interquartile range (IQR) 3–6 mg/kg/day] over a median period of 42 days (IQR 1.57–42 days). The median administered therapeutic dose was 6 mg/kg/day (IQR 5–6 mg/kg/day) over a median duration of 42 days (IQR 14–67 days). Therapeutic indications were invasive candidiasis, taenia capitis, fungal meningitis, urinary tract infection and other mycotic infections. The duration of treatment ranged between 1 day [40–42] and 9 years [68]. The most common routes of administration were oral (30 %), IV (23 %) or both (28 %) (Table 1).

Toxicity

A total of 4,209 patients from 90 studies were exposed to fluconazole, with 794 AEs recorded in 35 studies. Hepatotoxicity was the most common AE across all age groups. About one-third of the reviewed articles exclusively involved preterm and term neonates, accounting for 2,434 fluconazole exposed neonates. A total of 307 AEs (38.6 %) were recorded in neonates, of which 295 (96.1 %) were hepatotoxic effects. Gastrointestinal events were the second most common AE documented. One hundred cases of respiratory symptoms were recorded in one study, none of which was found to be drug-related. Other adverse events identified were renal dysfunction, haematological abnormalities and rash (Table 2). The relative risk of all AEs in the fluconazole group was not statistically different from those treated with placebo (RR 1.30, 95 % CI 0.84–2.03, *P*=0.238). Compared to all other antifungal drugs there was again no significant increase in the risk (RR 1.05, 95 % CI 0.62–1.80, *P*=0.85) (Fig. 2a). The overall relative risk of adverse events in the fluconazole group was not significantly different within the treatment group (RR 0.82, 95 % CI 0.49–1.36, *P*=0.437) or the prophylaxis group (RR 1.68, 95 % CI 0.55–5.11, *P*=0.364) compared to other antifungal drugs. There were 378 recorded cases of hepatotoxicity, accounting for just under half of all the AEs across all age groups. The majority

Fig. 1 Flow chart for articles included in the systematic review. *CINAHL* Cumulative Index to Nursing and Allied Health Literature, *RCTs* randomised controlled trials



of cases (295) occurred in neonates. The relative risk of hepatotoxicity with fluconazole was 1.36 (95 % CI 0.87–2.14) and 1.43 (95 % CI 0.67–3.03) when compared with placebo and other antifungals, respectively (Fig. 2a and 2b); these relationships were not statistically significant ($P=0.175$ and 0.352 , respectively). However, when compared against nystatin, the only comparator to have sufficient numbers of patients for analysis, there was a significant increase in risk of hepatotoxicity with fluconazole (RR 1.92, 95 % CI 1.13–3.26, $P=0.016$) (Fig. 2c).

Poisson regression analysis of the effect of treatment, age group, dose, route of administration, indication and duration of treatment on the incidence of hepatotoxicity of fluconazole was performed. This showed that the incidence of hepatotoxicity with therapeutic fluconazole was significantly greater than that with prophylaxis (IRR 5.34 95 % CI 1.99–14.37, $P=0.001$), while the duration of treatment had no effect. Although the incidence of hepatotoxicity in neonates on fluconazole was greater than that in children (IRR 1.33, 95 % CI 0.63–2.80), this effect was not statistically significant ($P=0.451$). The incidence of hepatotoxicity appears to decrease with increasing dose (IRR 0.52, 95 % CI 0.37–0.74, $P=0.001$). Patients on oral fluconazole were less likely to have hepatotoxicity than those on IV fluconazole (IRR 0.21, 95 % CI 0.92–0.47, $P=0.001$).

Only three of the cohort studies reported any AE; one of which was a prophylactic study which recorded 127 cases of cholestasis in 409 fluconazole-exposed extremely low birth weight neonates. However, this study did not report the number of non-exposed neonates. Of these patients, 69 % recovered, while the others were discharged or transferred to other facilities [36]. Another prophylactic cohort study recorded 60 cases of cholestasis in 140 fluconazole-exposed extremely low birth weight neonates as against 12 in 137 non-exposed neonates ($P<0.001$) [34].

Of all the 378 hepatotoxicity cases, resolution of symptoms was not determined in 113 (30 %) cases, while in 42 (11 %) cases, all involving neonates, there was no improvement at discharge or upon referral to another hospital (188 neonates and 35 children had completely recovered during treatment or shortly after). Therefore, 84 % of patients, for whom follow-up was complete, had resolution of symptoms. Hepatotoxicity was the most frequent reason for withdrawal of the drug. Of the 41 drug-related withdrawals, 17 (42 %) were due to elevated liver enzymes [26, 27, 30, 36, 42, 66, 69].

Gastrointestinal (GI) symptoms including nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, anorexia and gastritis accounted for 15.4 % of AEs (122 cases) (Table 2). There was only one recorded case of GI event in neonates.

Table 1 Summary of the 90 studies that reported on the safety of fluconazole in paediatric populations included in this review

Characteristics of studies	Number of studies	Number of patients
Type of study	<i>n</i> =90	<i>n</i> =4,209
Case series	23	795
Case reports	38	65
RCT	14	1,793
Cohort studies	7	1,564
Pharmacokinetics studies	8	77
Route of Administration	<i>n</i> =90	<i>n</i> =4,209
Oral	27	1,465
Intravenous and oral	26	1,602
Intravenous	21	971
Not reported	13	170
Intraperitoneal/rectal	3	15
Age groups	<i>n</i> =90	<i>n</i> =4,209
Preterm neonates	20	2,354
Term neonates	7	43
Term and preterm neonates	4	37
Other paediatric age groups ^a	59	1,775

RCT, Randomised controlled trial

^a Including studies involving infants up to adolescence (some of which included some neonates) and paediatric studies for which the age group was not stated

There was no statistical difference in the risk of GI events of fluconazole compared with placebo (RR 0.81, 95 % CI 0.12–5.60, *P*=0.831). The risk of GI events increased, but not significantly, when fluconazole was compared with other comparator antifungal drugs (RR 1.23, 95 % CI 0.88–1.71, *P*=0.235) and nystatin (RR 2.02, 95 % CI 0.66–6.23, *P*=0.219). Poisson regression analysis showed that the incidence of GI AEs were lower in neonates than children (IRR 0.15, 95 % CI 0.03–0.66, *p*=0.012), while dose (IRR 1.07, 95 % CI 0.85–1.39, *P*=0.585) and duration of treatment (IRR 1.01, 95 % CI 0.99–1.03, *P*=0.07) were unlikely to significantly affect the incidence of GI events. Although oral administration increased the incidence of GI AEs, this increase was not significant (IRR 3.22, 95 % CI 0.72–14.33, *P*=0.125).

There was a decrease in mortality when fluconazole was compared with placebo, but this was not significant (RR 0.62, 95 % CI, 0.38–1.03, *P*=0.067). The mortality rate between the fluconazole group and antifungal drugs was not different (RR 1.01, 95 % CI 0.72–1.41, *P*=0.960) (Table 3). No cases of drug-related death were documented. There were ten reported cases of serious AEs, five of which were not treatment-related [30]. The other serious AEs were five drug interactions [70–74]. Two interactions in children were with all-trans retinoic acid (ALTRA) and resulted in acute renal failure and pseudotumour cerebri [70, 71]. Another case of acute renal failure in a 9-year-old child was recorded following interaction with tacrolimus [73]. A 12-year-old child had syncope following co-administration

Table 2 Reported adverse events from 35 studies

Adverse events	Preterm neonates only	Term and preterm neonates	Infancy–adolescence	Others ^a	Total
Conjugated bilirubin	231	4	1	–	236
↑Liver enzymes	55	13	47	16	131
Respiratory infection ^b	–	–	100	–	100
GIT symptoms ^c	–	–	55	–	55
Headache	–	–	24	–	24
Vomiting	–	1	20	1	22
Abdominal pain	–	–	18	–	18
Other skin conditions	–	–	21	–	21
Rash/urticarial	–	–	19	–	19
Diarrhoea	–	–	16	1	17
Nausea	–	–	10	–	10
Eosinophilia	–	6	1	1	8
Altered renal function	–	3	4	–	7
Electrolyte derangement	2	–	–	–	2
Pruritus	–	–	6	–	6
Thrombocytopenia	5	–	–	–	5
Anaemia	–	2	–	–	2
Others	–	–	109	2	111
Total	293	29	451	21	794

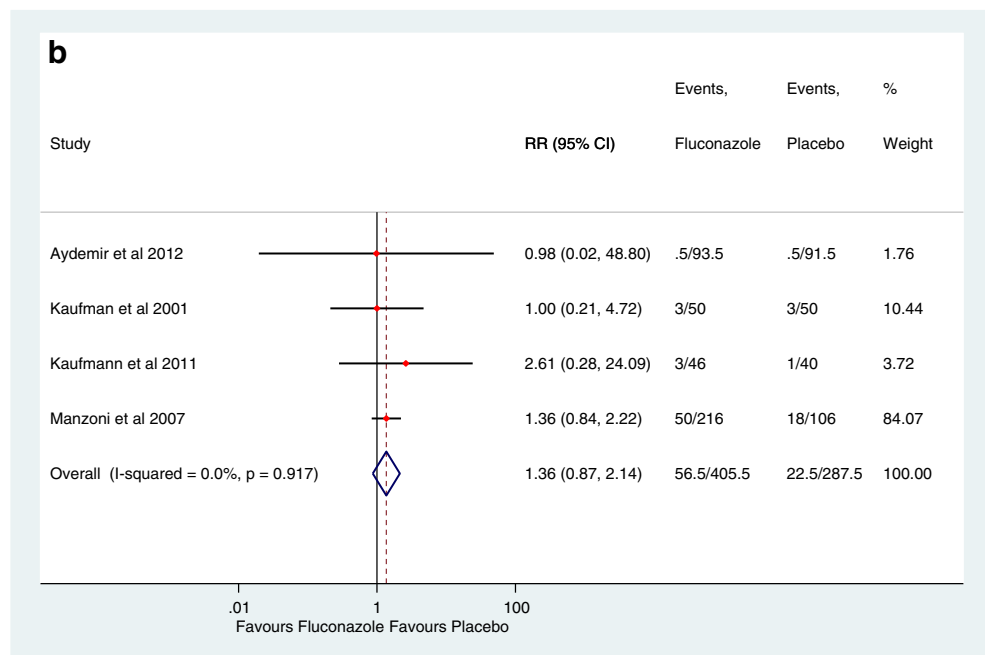
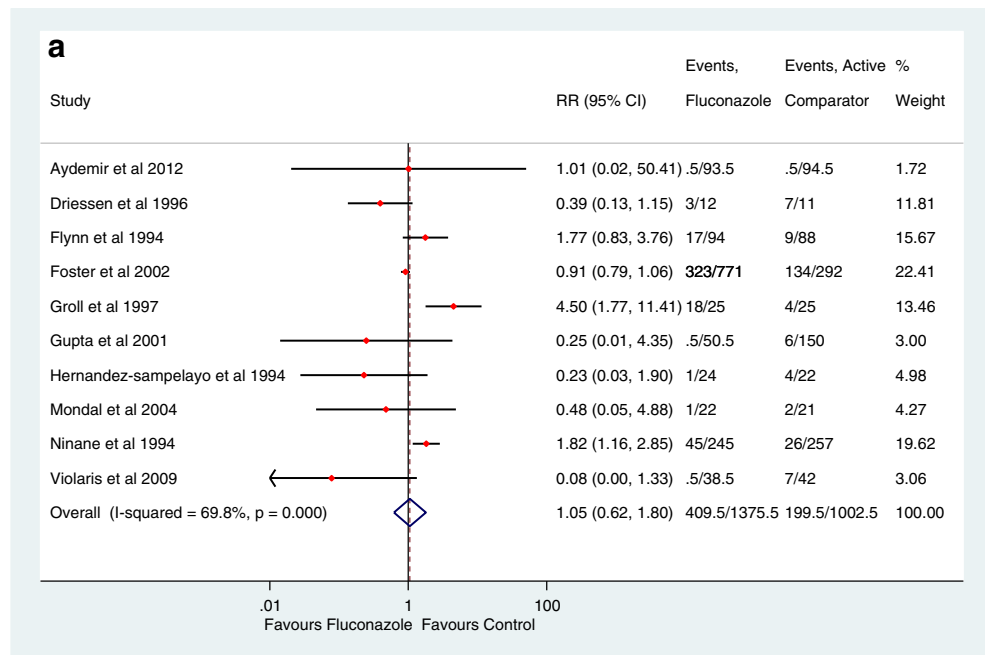
GIT, Gastrointestinal tract

^aNumber of adverse events (AEs) cut across age categories

^bObtained from a single study

^cPatients with anorexia, gastritis, dyspepsia, GI upset or a combination of any of nausea, vomiting, diarrhoea and abdominal pain

Fig. 2 a Fluconazole adverse effects (AEs) compared to those of other antifungals.
b Fluconazole hepatotoxicity compared with that of placebo.
c Fluconazole hepatotoxicity compared with that of nystatin



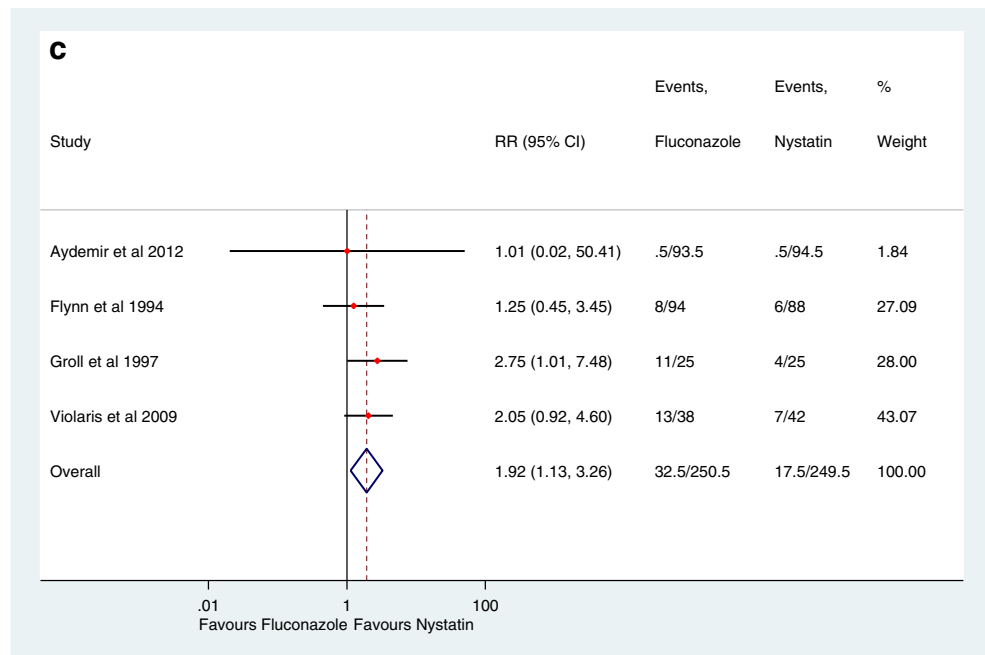
with amitriptyline [72]. Co-administration of fluconazole with vincristine also caused severe constipation [74].

Discussion

Hepatotoxicity was the most frequent AE described in this systematic review of the safety of fluconazole. It usually manifested as conjugated hyperbilirubinaemia or deranged liver enzymes and was also the most frequent reason for withdrawal of fluconazole in both neonates and paediatric

patients. Our review demonstrated that over 80 % of the cases with known outcomes had complete resolution during treatment or after completion of therapy. Hepatotoxicity risk was significantly greater in patients on fluconazole compared with nystatin ($p=0.016$). The better safety of nystatin compared with fluconazole has also been described by previous authors [75]. There was an increased risk of hepatotoxicity with fluconazole than placebo, but this increase was not significant ($p=0.175$). Prematurity, total parenteral nutrition, infection and congenital abnormalities are known risk factors for hepatotoxicity in neonates [76]. More neonates than

Fig. 2 (continued)



children developed hepatotoxicity, even though this incidence was not significantly different. Although animal studies have demonstrated a dose-dependent histological evidence of hepatotoxicity [77], this review did not show any significant effect of increasing dose on liver toxicity, probably because most of the reviewed articles administered fluconazole within the therapeutic dose limit of ≤ 12 mg/kg.

Our review also showed that GI events were the second most common AE after hepatotoxicity; however, the relative

risk of this event is not statistically different between patients on fluconazole and placebo or other antifungals. There was just one recorded case of a GI AE in neonates. This may be related to the fact that neonates are unable to self-report these events, and GI events are less likely to be identified by clinicians and parents. Nausea and abdominal pain, for example, are extremely difficult, if not impossible to detect in this age group.

Drug interactions with fluconazole have been documented. Fluconazole is a potent inhibitor of CYP enzymes and is known to inhibit both CYP3A and CYP1A2 enzymes [78]. Therefore, drug interactions with medicines such as tacrolimus, vincristine, ALTRA, midazolam, caffeine and amitriptyline are likely. Clinicians need to be aware of these interactions and monitor for AEs.

The relatively small number of patients in several of the groups for meta-analysis requires that these results be interpreted with caution. There were very few placebo controlled RCTs—a pool of which involved fewer than 500 patients. Such a small number may be insufficient to detect rare events. Additionally, the majority of the RCTs are primarily efficacy studies with poor and inconsistent reporting of safety outcomes. We excluded about 25 % of the identified RCTs because of their poor quality of safety reporting. Some of these limitations were also identified in several studies evaluating the quality of safety reporting in RCTs [79, 80]. Authors often fail to indicate the severity of the AEs and, in several cases, the relationship with medication was not determined. In addition, the duration of observation and outcome of AEs were often not established, with about 30 % of cases of hepatotoxicity not followed up to identify whether resolution had occurred. Comparison of fluconazole with other

Table 3 Effect of fluconazole compared with placebo, nystatin and active comparator

	Relative risk	95 % confidence interval	P value
Placebo			
Hepatotoxicity	1.37	0.87–2.14	0.175
GI events	0.81	0.12–5.59	0.831
Mortality	0.62	0.37–1.03	0.067
Withdrawal due to AE	0.78	0.08–7.24	0.828
Other antifungals			
Hepatotoxicity	1.43	0.67–3.03	0.352
GI events	1.23	0.88–1.71	0.235
Mortality	1.01	0.72–1.41	0.960
Withdrawal due to AE	1.25	0.62–2.53	0.534
Nystatin			
Hepatotoxicity	1.92	1.13–3.26	0.016*
GI events	2.02	0.66–6.23	0.219
Mortality	1.01	0.02–50.41	0.825
Withdrawal due to AE	1.01	1.11–9.59	0.992

* (<0.05) statistically significant

antifungal agents, except nystatin, was also impossible because of the paucity of good quality studies. Further research should include studies with extended follow-up to capture data regarding the resolution of hepatotoxicity, especially in the neonatal population.

In conclusion, fluconazole is relatively safe for paediatric patients. Hepatotoxicity and GI events are the most common AEs. It is important to be aware that drug interactions with fluconazole can result in significant toxicity [81–111].

Acknowledgements This work is part of the TINN network (Collaborative Project) supported by the European Commission under the Health Cooperation Work Programme of the 7th Framework Programme (grant agreement no. 223614).

Funding This research was conducted within the framework of a TINN project, a FP7 project sponsored by the European Commission.

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