Seizures and quinolone antibiotics in children: a systematic review of adverse events

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ABSTRACT

Background Quinolone antibiotics have a broad spectrum of activity including against Gram-negative organisms (especially *Pseudomonas*), but their use has been associated with the development of seizures. Our objective was to evaluate the association between the administration of quinolones and seizures for three groups of children: those with epilepsy; those with other CNS disorders; and those without any CNS disorder.

Method We conducted a systematic review of the MEDLINE, EMBASE and CENTRAL databases. Any studies reporting the administration of quinolones to children and including a methodology for identifying or reporting adverse events were identified by two authors who worked independently. Data relating to study characteristics (including population, intervention, comparison and outcome data) and study quality (including the quality of adverse event reporting) were extracted.

Results We identified 140 studies involving 21 884 children. No studies reported involving children with epilepsy and 21 studies reported the involvement of 317 children with CNS disorders. 2/317 (0.63%) children with CNS disorders developed seizures and at least 4/21 567 (0.023%) children without CNS pathology were reported to have developed seizures. The quality of adverse event reporting in included studies was low. Only 8/140 (5.71%) included studies provided details of a methodology for actively identifying adverse neurological events.

Discussion Even for children with CNS disorders the risk of developing seizures in association with the use of quinolones seems to be low. Further evaluations of quinolone use in children should include methodologies for actively identifying and reporting adverse neurological events.

INTRODUCTION

Quinolone and fluoroquinolone antibiotics are bactericidal agents that target bacterial DNA replication. They have a broad spectrum of activity against both Gram-negative and Gram-positive organisms, high bioavailability from oral preparations, and are the only oral anti-pseudomonal agent. Children with neurological disorders are recognised to be at higher risk of developing infections that would often be susceptible to treatment with quinolone antibiotics.[1 2] However, there are concerns that quinolones may lower the seizure threshold and, in the USA and UK, quinolones (such as ciprofloxacin) are only licensed for use in children in certain circumstances. Examples include the treatment of complicated urinary tract infections and pseudomonal infections in cystic fibrosis.[3 4]

Concerns that quinolones may lower the threshold for seizures have been linked to their chemical structure. Norfloxacin and ciprofloxacin contain gamma-aminobutyric acid (GABA)-like structures in substituents at their 7 positions. These structures may act as antagonists of GABA receptors, thereby increasing the likelihood of seizures, as demonstrated using mouse models.[5–7] However, these findings have not been reproduced in studies investigating the administration of quinolones to adults.[8 9] In children, data from the UK Medicines and Healthcare products Regulatory Agency (MHRA) adverse events 'yellow card' reporting service have also provided limited evidence associating quinolone use with seizures in children. A review of MHRA drug analysis profiles identified 13 submissions reporting non-fatal seizures in children associated with the use of quinolones since 1987 (identified using a search of MHRA drug analysis profiles[10]).

The aim of this study was to review the association between the use of quinolones and the development of seizures in children in order to help clinicians assess the risks and benefits of their use. These risks were evaluated using a systematic review of published literature designed to identify any reports of seizures associated with the use of quinolones in three groups of children:

1. Those known to have epilepsy.
2. Those at higher risk of developing seizures due to associated CNS disorders of any aetiology (including infectious, congenital, developmental, traumatic or neoplastic disorders).
3. Those without a history of epilepsy or other CNS disorders.

METHODS

The Medline, Embase, Pubmed and Cochrane Central Register of Controlled trials (CENTRAL) databases were searched (from inception until November 2017) to identify studies reporting the administration of quinolones to children (from birth at any post-menstrual age to less than 18 years), where the authors also reported an assessment of safety through the active or passive identification of adverse events (AEs) (see online supplementary file for full search strategy). Two authors independently screened the titles and abstracts to identify full texts for consideration for inclusion in the review. We included any studies meeting the inclusion criteria including randomised controlled trials, observational studies and case reports.

We excluded studies where quinolones were not administered either orally or intravenously and,

due to time and resource constraints, we excluded non-English language studies.

Bibliographies of systematic reviews, meta-analyses and review papers identified from the initial strategy were subsequently hand searched to identify additional studies that met the inclusion criteria.

The protocol for this investigation was based on accepted methodology for identifying and reporting adverse events using systematic review and was agreed a priori.[11 12] Following the initial searches and further discussion among the group, we agreed to exclude studies from the final analysis if:

- They included children but it was not possible to separate data relating to children and adults from the published results.
- Studies described a methodology that would preclude investigators from identifying seizures as an associated adverse event; for example, using follow-up X-rays to identify joint pathology or searching registries for episodes of joint pathology following quinolone administration.

In keeping with a recognised framework for using systematic review methodology to report AEs (where AEs are often identified and reported using heterogeneous methods),[11] we included any descriptions of seizures associated with the use of quinolones as the primary outcome of interest. A secondary evaluation, that included the assessment of factors such as the likelihood that reported seizures were related to the administration of quinolones, was completed as part of the quality assessment and is described below.

Data extraction

Included papers were interrogated to identify study characteristics, population, intervention, comparison and outcome (PICO) data (including details of individuals known to have epilepsy

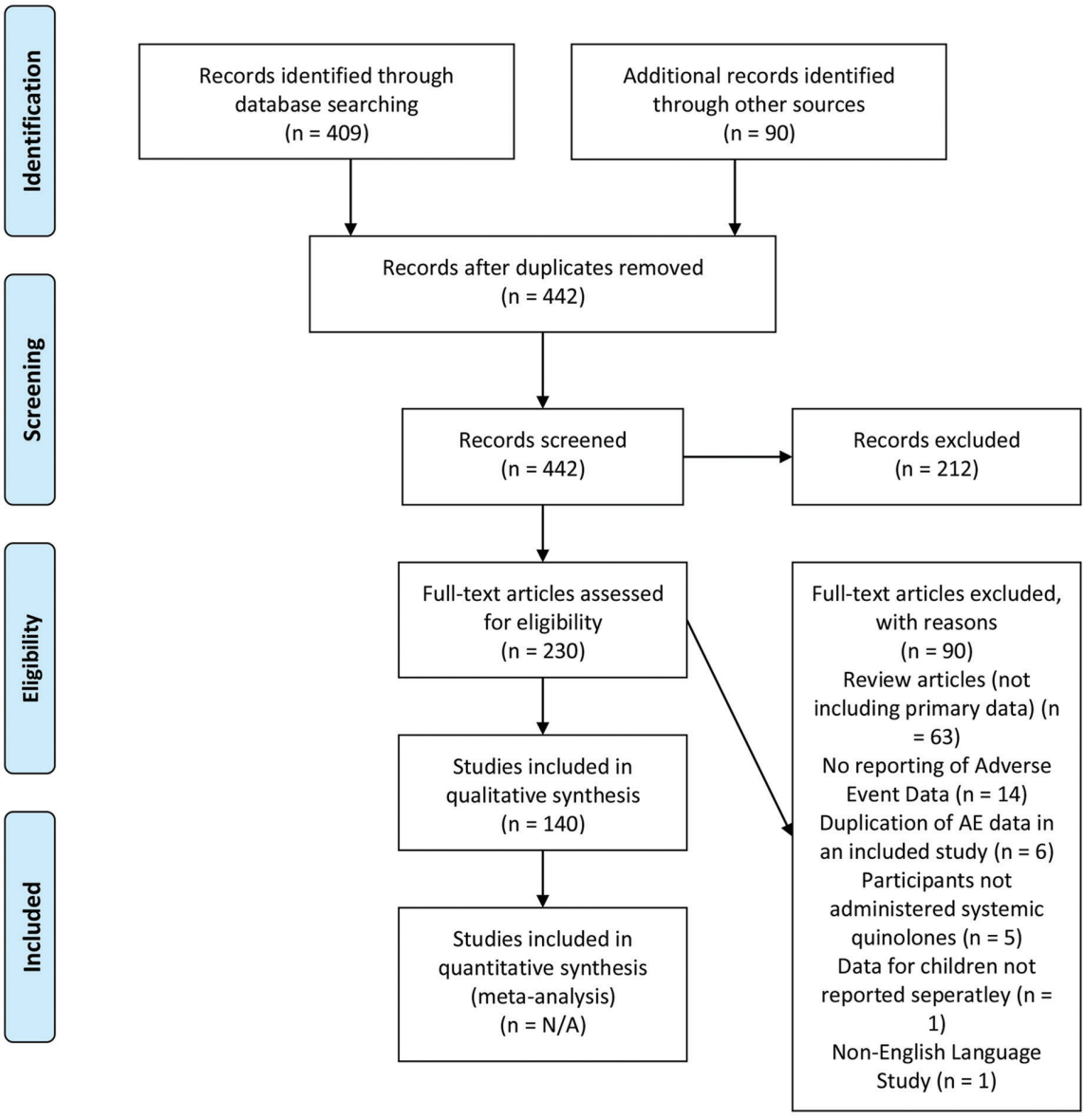

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Figure 1 PRISMA flow chart outlining study selection process.

or other CNS disorders) and study methodology. Randomised controlled trials were assessed for bias based on evidence of the quality of randomisation, allocation concealment and blinding. The quality of AE reporting was assessed for all studies based on the rigour with which investigators described methodologies for actively identifying and reporting AEs. We also noted whether investigators had reported a methodology for identifying neurological AEs. When seizures were reported we assessed whether the investigators had used a recognised methodology for determining the likelihood that they were causally related to the use of quinolones.

Data analysis

Given the likely heterogeneity of studies eligible for inclusion in the review, we planned to report our findings using a narrative synthesis.

RESULTS

The search strategy identified 140 studies for inclusion in the review (see figure 1, PRISMA flow chart for full details of excluded studies; see online supplementary file for a list of included and excluded studies (studies excluded following a review of the full text)).

Thirty-two studies were randomised controlled trials, 75 were observational studies and 33 were case reports or case series. The included studies reported data relating to 33 718 participants, 21 884 of whom were children who had been administered quinolones in 22 714 treatment episodes. Included studies involved children of all ages, ranging from preterm infants with a post-menstrual age of 24/40 weeks up to 17-year-olds (see Study Characteristics table in online supplementary file for summarised PICO data).

Types of quinolones administered to the study population

Ciprofloxacin was the most widely used quinolone (n=16 633), followed by levofloxacin (n=2739) and gatifloxacin (n=1157) (see table 1 for full list of administered antibiotics and dosing ranges prescribed).

Table 1 Dosing ranges and administration routes for included quinolones

Quinolone	Number of children who received quinolone	Dosing and administration information
Ciprofloxacin	16 633	IV: dosing range 8–30 mg/kg/day up to 500 mg/day PO: 10–40 mg/kg/day or up to 1.5 g/day
Levofloxacin	2793	IV: dosing range 7–25 mg/kg/day up to 500 mg/day PO: 10–40 mg/kg/day
Gatifloxacin	1157	PO: 10–15 mg/kg/day
Ofloxacin	790	PO: 10–40 mg/kg/day up to 400 mg/day
Trovofloxacin	162	IV: 5 mg/kg/day
Moxifloxacin	32	PO: 10 mg/kg/day up to 400 mg/day
Nalidixic acid	30	PO: 50–220 mg/day
Norfloxacin	24	PO: 20–30 mg/day
Pefloxacin	12	IV: 12 mg/day PO: 12.5 mg/kg/day

IV, intravenous administration; PO, oral administration.

Overall result

The administration of oral or intravenous quinolones was only rarely associated with the development of seizures (overall incidence of confirmed reported seizures 6/21 884 participants (0.03% of children)).

Studies involving children with epilepsy

No studies reported the involvement of children known to have epilepsy.

Studies involving children with CNS disorders

Twenty-one studies reported the inclusion of 317 children with CNS disorders (see table 2). . Bacterial meningitis was the most frequently reported CNS disorder (n=237), followed by CNS malignancies (n=29) and infants with grade III or IV intraventricular haemorrhage (n=19). In one study 22 children with neurological disorders not otherwise specified were reported to have received quinolones, but no further details of their CNS disorder were provided.

Seizures occurred in 2/317 children who were reported to have an associated CNS disorder. One child had confirmed *Haemophilus influenzae* meningitis and the authors of the case report commented that the prior administration of trovofloxacin was unlikely to have been the cause of the child's seizure. This occurred 11 days after trovofloxacin had been discontinued. One child had leukaemia and cryptococcal meningitis but the authors did not comment on an association between gatifloxacin and the seizure. Neither case report indicated a standardised

Table 2 Summary of indications and underlying conditions described in included studies

Type of infection	Number of children	Underlying condition	Number of children
Gastrointestinal infection including enteric fever	6043	Cystic fibrosis, most cases with associated pulmonary exacerbation	995
Otitis media	2706	Paediatric cancers	1019
Community acquired pneumonia	1935	Post haematopoetic stem cell transplantation	265
Prophylaxis	979	Chronic renal disease	20
Febrile neutropenia	593	Neurological disorders	22
Neonatal sepsis	591	Intraventricular haemorrhage (Grades III-IV)	19
Central nervous system	245	CNS malignancy	29
Cellulitis	227	Congenital cyanotic heart disease	2
Tuberculosis	67	Head injury	2
Bacteraemia	100	Leukaemia and *Cryptococcus neoformans* meningitis	1
BK viraemia	19	Myelitis	1
Bone or joint	23	Bare lymphocyte syndrome	1
Cholangitis	13	Inflammatory bowel disease	1
Tularaemia	12	Major histocompatibility complex class II deficiency	1
Infection of prosthetic cardiac device	2	Sacral agenesis	1
Rhinoscleroma	1		
Other/indications not described in detail	7343		

Table 3 Characteristics of children who presented with seizures in association with the use of quinolones

Age	M/F	Medical history	Reason for quinolone use	Quinolone	Dosing and administration	Association with quinolone use	Quinolone discontinued	Outcome
Children with CNS disorders who developed seizures								
8 months	M	Pneumonia, herpes stomatitis, hepatitis, diseminated intravascular coagulation	*Haemophilus* meninigitis	Trovofloxacin	5 mg/kg loading dose, then 2.5 mg/kg 12-hourly IV	Unlikely; seizure developed 11 days after stopping trovafloxacin	No	No long-term morbidity
N/A	N/A	Leukaemia and *Cryptococcus neoformans* meningitis	Febrile neutropaenia	Gatifloxacin	15 mg/kg 24-hourly PO	N/A	N/A	N/A
Children without CNS disorders who developed seizures								
1.25 years	M	Pneumonia	Pneumonia	Ciprofloxacin	10 mg/kg 12-hourly IV	Possible	N/A	No long-term morbidity
3 months 24 days	F	Bronchiolitis	Pneumonia	Ciprofloxacin	10 mg/kg 12-hourly IV	Unlikely	Yes	No long-term morbidity
N/A	N/A	N/A	Pneumonia	Levofloxacin	10 mg/kg 12-hourly (administration details not provided)	Possible; described as a 'febrile convulsion'	N/A	N/A
2.5 years	N/A	N/A	*Shigella flexneri* enteritis	Ciprofloxacin	10 mg/kg 12-hourly PO	N/A	N/A	N/A

N/A, data not available; IV, intravenous administration; PO, oral administration.

methodology for grading the likelihood that seizures were related to the administration of quinolones.

Studies involving children without CNS pathology

A total of 119 studies reported the inclusion of 21 567 children without reported CNS disorders (see table 2 for a summary of the indications for the use of quinolones). At least 4/21 567 (0.023%) children developed seizures in association with the administration of quinolones; their clinical features are summarised in table 3. In one study reported as a conference abstract involving 165 neonates treated with quinolones the authors reported that some infants developed seizures; however, specific details regarding the numbers of affected infants were not provided.[13]

In two cases the investigators felt that the seizure was possibly related to the use of quinolones,[14 15] in one case this was felt to be unlikely[14] (one child had presented with seizures prior to initiation of ciprofloxacin) and in one case no comment was made with regard to the possibility of a causal relationship.[16] In one case the prescribed quinolone was withheld following the seizure episode and in four cases it was not clear whether the quinolone therapy was discontinued by the investigators. None of the authors reported the use of a standardised system for grading the likelihood that the described AEs were related to the use of quinolones.

Other adverse events

The most frequently reported AEs described in association with the use of quinolones included nausea and vomiting (n=916, 4.60% of participants), diarrhoea (n=661, 3.34% of participants) and rash (n=606, 3.03% of participants) (see table 2 for a summary of the most frequently reported adverse events). Joint symptoms were identified in 482 children (2.41% of participants). We note that seizures were reported less frequently than other AEs including episodes of acute kidney injury (n=48; 0.22% of children administered quinolones). A summary of reported adverse events is presented in table 4.

Quality of adverse event reporting

All of the studies included in the analysis involved either active or passive monitoring for AEs or, alternatively, the authors reported the presence or absence of AEs in the results or discussion sections of the paper. The authors of 92/140 (65.7%) included studies reported that AEs were actively sought during their investigation of the use of quinolones. The authors of 61/140 (43.6%) studies provided some methodological detail relating to the active identification of AEs. However, only 8/140 (5.71%) included studies provided details of a methodology describing the active identification of neurological AEs including seizures. Thirty-four of140 studies (24.3%) described methodologies for the active identification of AEs relating to joint pathology or abnormal growth.

DISCUSSION

To our knowledge this is the first systematic review designed to investigate the potential association between the use of quinolones and seizures in children. Evaluating the risks and benefits of using quinolones for children with CNS disorders may be particularly important because this group is likely to be at higher risk of developing resistant Gram-negative or hospital-acquired infections.[1 2] In these cases, the benefits of using highly bioavailable broad-spectrum quinolone antibiotics need to be balanced with a consideration of their risks.

A comparison of the incidence of seizures in children who were administered quinolones and reported to have associated

Table 4 Most frequently reported adverse events

Symptom	Number of children affected (%)
Nausea and vomiting	916 (4.6%)
Diarrhoea	661 (3.3%)
Rash	606 (3.0%)
Joint pain	482 (2.4%)
Elevated hepatic enzymes	228 (1.1%)
Abdominal pain	200 (1.0%)
Acute kidney injury	48 (0.2%)

CNS disorders (2/317; 0.63%) with the reported incidence of seizures in children who did not have associated CNS disorders (4/21 567; 0.02%) suggests that the risk of developing seizures seems to be small for both groups. However, this review has a number of limitations.

One limitation is that the majority of eligible studies were not designed with robust methods for identifying adverse neurological events such as seizures. Only 8/140 (5.71%) studies provided detail of a specific methodology for prospectively identifying these types of AEs. Another limitation is that none of the identified investigations reported the inclusion of children with epilepsy. Furthermore, only a minority of studies included participants who may have been predisposed to developing seizures due to CNS disorders including CNS infections, neurodisability or brain injuries.

In addition to limitations relating to the active identification of AEs in the included studies, we also identified evidence of selective reporting of outcomes or incomplete reporting of AE data (this occurred despite the requirement for all included studies to report the results of an AE analysis; please contact the authors to request the Study Quality Summary Table for further details). For example, the study that included the largest number of participants with associated CNS disorders was a randomised trial comparing trovofloxacin (now withdrawn from use) with ceftriaxone, with or without vancomycin, for the treatment of meningitis.[17] Although the authors reported a methodology for actively identifying seizures in participants, there was incomplete reporting of AEs (the authors reported a total of 437 AEs in the trovofloxacin group but only provided detail regarding 99 of these in the published report). In another study, reported as a conference abstract, seizures were identified in an unspecified number of infants but the authors provided no details regarding the total numbers affected, or whether the seizures were felt to be related to the administration of quinolones[13] (attempts to contact the study authors to obtain more detailed data regarding the outcomes of their investigation were made during the completion of this review).

CONCLUSION

The risk of developing seizures in association with the use of quinolones seems to be small. Future studies involving the use of quinolones in children would benefit from robust methodologies for actively identifying and reporting adverse neurological events. This would help to further quantify the risks associated with the use of quinolone therapy for children who may otherwise benefit from their use.

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Contributors MN designed the search strategy and data collection instruments, reviewed the identified titles, abstracts and articles for inclusion in the review, completed the data collection process, carried out the initial analyses and produced the initial manuscript. CK contributed to the development of the study protocol, reviewed the titles, abstracts and selected articles identified during the database searches to identify relevant studies for inclusion in the review and contributed significantly to the drafting of the initial manuscript. AR, RK and AI made substantial contributions to the analysis and interpretation of data and critically reviewed and revised the manuscript for important intellectual content. IS conceptualised the study, helped to prepare the review protocol and data collection instruments, coordinated and supervised data collection and critically reviewed and revised the manuscript for important intellectual content. DBH coordinated and supervised data collection and critically reviewed and revised the manuscript for important intellectual content.

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