Effects of MHRA drug safety advice on time trends in prescribing volume and indices of clinical toxicity for quinine

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Quinine is commonly prescribed in primary care for muscle cramps.
- Quinine is of limited efficacy in leg cramps and is associated with toxicity including visual and hearing impairment, cardiac arrhythmias and death, especially after overdose.
- The UK Medicines and Healthcare Products Regulatory Agency (MHRA) therefore published a safety update in June 2010 aiming to restrict the prescription of quinine for muscle and leg cramps, and thereby minimize the frequency of quinine toxicity.

WHAT THIS STUDY ADDS

- Growth in quinine prescribing has been arrested since the MHRA update, and the number of episodes of deliberate self-harm, moderate or severe cases of poisoning and other indices of quinine toxicity have also stabilized.
- Substantial reductions in quinine prescribing were achieved in areas where comprehensive local measures, such as information to patients on the efficacy and possible harm from quinine, review of all repeat prescriptions and the consideration of alternative therapies, were implemented in response to the update.
- Quinine prescribing, however, remains common and continues to expose the population to potentially serious adverse effects and toxicity.

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AIMS

To ascertain the effects of the Medicines and Healthcare products Regulatory Agency's (MHRA) safety update in June 2010 on the volume of prescribing of quinine and on indices of quinine toxicity.

METHODS

We analysed quarterly primary care total and quinine prescribing data for England and quinine prescribing volume for individual Primary Care Trusts in the North East of England from 2007/8 to 2011/12 obtained from the ePACT.net database. We also analysed quinine toxicity enquiries to the National Poisons Information Service (NPIS) via Toxbase® and by telephone between 2004/5 and 2011/12. Joinpoint regression and Pearson's correlation tests were used to ascertain changes in trends in prescribing and indices of toxicity and associations between prescribing and indices of toxicity, respectively.

RESULTS

Total prescribing continued to increase, but annual growth in quinine prescribing in England declined from 6.0 to -0.6% following the MHRA update [difference -0.04 (95% confidence interval -0.07 to -0.01) quinine prescriptions per 100 patients per quarter, $P = 0.0111$]. Much larger reductions were observed in Primary Care Trusts that introduced comprehensive prescribing reviews. The previously increasing trend in Toxbase® quinine searches was reversed [difference -19.76 (95% confidence interval -39.28 to -9.20) user sessions per quarter, $P = 0.0575$]. Telephone enquiries to NPIS for quinine have declined, with stabilization of the proportion of moderate to severe cases of quinine poisoning since the update.

CONCLUSIONS

The MHRA advice was followed by limited reductions in the growth in quinine prescribing and in indicators of quinine overdose and toxicity. Quinine prescribing, however, remains common, and further efforts are needed to reduce availability and use.

Introduction

Quinine is used in conjunction with other drugs for the treatment of falciparum malaria infection [1]. The bulk of quinine prescribing in the UK, however, occurs in primary care and is almost entirely for muscle cramps affecting the legs. Clinical trials and meta-analyses, however, have shown limited additional benefits from quinine for this indication over those associated with placebo use [2–4].

The use of quinine, especially in overdose, carries a risk of significant morbidity and mortality. In clinical trials, adverse effects commonly associated with quinine included headache, nausea and vomiting, tinnitus, dizziness, fever and pruritus [2–4]. Severe toxicity may include altered consciousness, convulsions, hypoglycaemia, deafness, peripheral visual field constriction, reduced visual acuity, blindness and cardiac arrhythmias [5, 6]. These are most common with doses above 3–4 g [5, 7], although an adult lethal dose of 1.5 g has previously been reported [8].

Adverse effects of quinine are not limited to cases of overdose. Between 1965 and 2006, the United States Food and Drug Administration (FDA) received reports on 665 cases of adverse events with serious outcomes from quinine use, including 93 deaths as well as cardiac arrhythmias, thrombocytopenia and hypersensitivity reactions. This informed the FDA's withdrawal order in 2006 of all quinine products used off-label for muscular cramps [9].

Despite its limited efficacy and potential toxicity in therapeutic use and in overdose [2–4, 6–8], quinine prescribing for muscle and leg cramps has been increasing. As a result, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a Drug Safety Update article on the use of quinine for the treatment of leg cramps in June 2010. This advised that the use of quinine for nocturnal leg cramps should be limited to severe cases, with careful selection, trial and monitoring of patients [10].

The aim of this study was to examine the effect of this Drug Safety Update on prescribing trends of quinine and on indices of quinine overdose and poisoning derived from quinine enquiries to the National Poisons Information Service (NPIS).

Materials and methods

Quarterly primary care total and quinine prescribing data for England and quinine prescribing volume for individual Primary Care Trusts (PCTs) in the North East of England for the financial years 2007/8 to 2011/12, corresponding to quarters for the calendar years April 2007 to March 2012, were obtained from the electronic Prescribing Analysis and Cost database (ePACT.net) held by the Prescription Pricing Division of the NHS Business Services Authority. ePACT.net allows analysis of prescribing data, including type, volume and cost of drugs, held on NHS Prescription Services' Prescribing Database over the previous 60

months, with the ability to limit enquiries to prescribing organizations (e.g. GP practice, PCT) or British National Formulary classification.

Data were also obtained on quinine enquiries from healthcare professionals to the NPIS via the password-protected Internet database Toxbase® and by telephone for the 2004/5 to 2011/12 financial years corresponding to calendar years April 2004 to March 2012. These served as indices of quinine toxicity and included gross numbers of user sessions involving access to the quinine entry on Toxbase® and the numbers of NPIS telephone enquiries relating to quinine. These indices were also standardized as proportions of all product accesses or telephone enquiries to correct for annual variations in the total number of Toxbase® accesses and telephone enquiries.

Time-related trends in prescribing and indices of toxicity were analysed on quarterly and annual bases, with comparisons made between the periods before (pre) and after (post) the MHRA safety update. We investigated the occurrence, timing and magnitude of changes in numbers of accesses to Toxbase®, total and quinine prescribing volume for England and quinine prescribing volume for individual PCTs in the North East of England with joinpoint regression analysis using SEER*Stat software version 3.5.3 (National Institutes of Health, National Cancer Institute, Surveillance Research Program, Division of Cancer Control and Population Sciences, Bethesda, MD, USA), which accounts for seasonal variation. Linear segment models were fitted with between zero and three joinpoints, and Monte Carlo permutation tests were used to choose the best-fitting model, including the number and position of the joinpoints, corresponding to the occurrence and timing of changes and the slopes of the trends [11]. Results are presented as differences in slopes (prescribing volume or numbers of accesses) with 95% confidence intervals (CIs) and *P* values for the null hypothesis that the slopes are the same. Associations between prescribing rates and Toxbase® enquiries were tested by Pearson's correlation using IBM SPSS version 19.0 (IBM United Kingdom Limited, Hampshire, UK). Annual variations in total and quinine prescribing for PCTs and England were derived by comparing the prescribing volumes of corresponding quarters in consecutive years. The PCTs have been anonymized and represented as PCT 'A' to PCT 'L'.

Results

Total and quinine prescribing volumes for England, as well as quinine prescribing volume for individual PCTs in the North East of England, showed a quarterly cyclical variation during each of the financial years under consideration, increasing from the first through to the third quarters and then declining in the fourth quarter to levels similar to those of the first quarter (Figure 1).

Figure 1

Prescribing trends for quinine in England (—) and Primary Care Trusts (PCTs) in the North East of England (—■— PCT 'A', —▲— PCT 'B', —◆— PCT 'C', —●— PCT 'D', + PCT 'E', □ PCT 'F', ◇ PCT 'G', ○ PCT 'H', △ PCT 'I', × PCT 'J', + PCT 'K', — PCT 'L') compared with total prescribing volume in England (---) from 2007/8 to 2011/12. The publication of the MHRA safety update on quinine is depicted by ↑

Prior to the publication of the MHRA safety update, quinine prescribing in England was increasing, but it has since stabilized, with evidence of a difference in time trends before and after the MHRA safety update [estimated time of change, second quarter 2010/11 (95% CI, first quarter 2009/10 to fourth quarter 2010/11); difference, -0.04 (95% CI, -0.07 to -0.01) quinine prescriptions per 100 patients per quarter; $P = 0.0111$; Figure 1].

Comparison of corresponding quarters of consecutive financial years showed a consistent annual increase in quinine prescribing of 6.0% from 2007/8 until the MHRA update in June 2010. Since then, there has been a significant change, with a mean annual reduction of 0.6% [estimated time of first change, fourth quarter 2009/10 (95% CI, second quarter 2009/10 to second quarter 2010/11); difference, -1.89 (95% CI, -3.10 to -1.23) percentage change in quinine prescriptions per 100 patients between corresponding quarters of consecutive years; $P = 0.0157$]. Quinine prescribing continued to decline after the update and was most marked in the second quarter of 2011/12; more recent data, however, exhibit a reversal in this trend [estimated time of second change, fourth quarter 2010/11 (95% CI, second quarter 2010/11 to second quarter 2011/12); difference, 1.80 (95% CI, 0.41 – 2.55) percentage change in quinine prescriptions per 100 patients between corresponding quarters of consecutive years; $P = 0.0343$; Figure 2]. In contrast, total prescribing in England continued to increase at a steady rate of 4.0% (95% CI, 2.4–5.2)

between 2008/9 and 2011/12, with no change in trend (zero joinpoints) in spite of the safety update.

In PCT 'D', comparison of the corresponding quarters of consecutive years showed a sequential decline in prescribing volume of 21.6–68.8% from the second quarter of 2010/11 to the fourth quarter of 2011/12, resulting in a decline in prescriptions from 2.63 items per 100 patients immediately before the MHRA safety update to 0.76 items per 100 patients at the end of the 2011/12 financial year [estimated time of change, first quarter 2010/11 (95% CI, third quarter 2009/10 to second quarter 2010/11); difference, -0.63 (95% CI, -0.91 to -0.49) prescriptions of quinine per 100 patients; $P = 0.0006$]. Prescribing stabilized in most other PCTs, although increasing trends continued to be observed in some, including PCT 'E' and PCT 'L' (Figure 1).

Leading up to June 2010, when the MHRA safety update on quinine was published, Toxbase® user sessions for quinine were increasing, but there has subsequently been a declining trend [estimated time of change, third quarter 2010/11 (95% CI, fourth quarter 2005/6 to second quarter 2011/2); difference, -19.76 (95% CI, -39.28 to -9.20) Toxbase® user sessions for quinine per quarter; $P = 0.0575$]. Gross quarterly quinine Toxbase® user sessions correlated significantly with corresponding quarterly prescribing volume for quinine over the same time period (correlation coefficient = 0.5594; P value = 0.0103; Figure 3). Trends in NPIS telephone enquiries involving quinine were

Figure 2

Changes in prescribing volume between corresponding quarters of consecutive years for quinine prescribing (□) and for total prescribing (■) in England from 2008/9 to 2011/12. ↑ depicts the publication of the MHRA safety update on quinine

Figure 3

Total (▲) and standardized (△) annual Toxbase® quinine user sessions as indices of quinine poisoning in the UK compared with total quinine prescriptions in England (■). Standardized annual Toxbase® enquiries were derived as a ratio of total quinine to total Toxbase® enquiries. The order of withdrawal of unapproved 'off-licence' quinine products for muscle cramps by the USA FDA and the publication of the MHRA safety update for quinine are represented by ↓ and ↑, respectively

similar to those for Toxbase® user sessions (Figure 4), although numbers were not large enough for detailed statistical evaluation.

Nationally, the NPIS received 510 telephone enquiries involving quinine poisoning between 2008/9 and 2011/12.

Of these, 290 (56.9%) related to accidental use or therapeutic error and, of these, 222 (76.6%) were not associated with any reported adverse effects. The dose of quinine ingested was known in 219 (75.5%) of the cases of accidental use or therapeutic error, of which 188 (85.8%)

Figure 4

Total (▲) and standardised (△) telephone enquiries on quinine to the National Poisons Information Service (NPIS) as indices of quinine poisoning in the UK compared with total quinine prescription in England (—■—). Standardized telephone enquiries were derived as a ratio of quinine enquiries to total telephone enquiries. The publication of the MHRA safety update for quinine is represented by ↑

Table 1

Characteristics of National Poisons Information Service telephone enquiries relating to quinine

	2008/9	2009/10	2010/11	2011/12
Self-harm [n (%)]	53 (39%)	63 (43%)	34 (32%)	46 (38%)
Cardiac toxicity [n (%)]	18 (13%)	33 (22%)	29 (28%)	26 (21%)
Visual impairment [n (%)]	17 (13%)	26 (18%)	16 (15%)	14 (11%)
Hearing impairment [n (%)]	10 (7%)	6 (4%)	3 (3%)	13 (11%)
Cardiac, visual or hearing impairment (events) [n (%)]	45 (33%)	65 (44%)	48 (46%)	53 (43%)
Cardiac, visual or hearing impairment (patients) [n (%)]	39 (29%)	39 (27%)	34 (32%)	31 (25%)
Total number of cases (n)	136	147	105	122

were ≤ 0.9 g. Self-harm accounted for 196 (38.4%) of all cases, with a median reported ingested dose (range) of 4.4 (0.9–19.0) g. Of the cases of self-harm, 163 (83.2%) were symptomatic, representing 68% of all cases of quinine-associated toxicity reported by telephone to the NPIS. The incidences of deliberate self-harm and serious toxic features associated with overdoses involving quinine are shown in Table 1, and the severity of episodes of quinine poisoning is shown in Figure 5. Other serious clinical features reported to NPIS over this 4 year period included acidosis ($n = 28$), stupor or coma ($n = 18$), hypoglycaemia ($n = 8$), convulsions ($n = 4$), agitation ($n = 3$) and death ($n = 2$).

Discussion

Our analysis demonstrates that the MHRA safety update on quinine has stabilized the volume of quinine prescribed

Figure 5

Poisons Severity Scores for cases of quinine poisoning reported to the National Poisons Information Service from 2008/9 to 2011/12. □, 2008/9; ▨, 2009/10; ▩, 2010/11; ■, 2011/12

in England during a period when total prescribing volume continued to increase. The effect on prescribing volume of quinine has been associated with a downward trend in Toxbase® indices of quinine poisoning, and the data suggest an initial decline and subsequent stabilization in the number of cases of moderate or severe episodes of quinine poisoning reported in telephone enquiries to the NPIS (Figure 5). There is, however, evidence that the impact of the MHRA safety update on quinine prescribing is now waning after nearly 2 years (Figure 2). Cases of quinine overdose or poisoning, although infrequent, continue to be an important source of morbidity and mortality, with cardiac complications, hearing impairment or visual impairment documented in a third of patients with quinine overdose reported to the NPIS. These findings are consistent with those previously reported for Scotland [7].

There are several limitations, however, to the data presented in this study. The prescribing data from ePACT.net are not linked to diagnosis and reflect only primary care prescribing, excluding private prescriptions and those dispensed in hospitals or mental health units. Primary care prescribing will, however, incorporate the great majority of quinine prescribing in the UK, and indications other than leg cramps are rare. Prescription numbers are not a direct measure of the numbers of patients exposed, because durations and doses may vary, but are useful for following time trends. TOXBASE® access data are not necessarily case specific, accesses may be made for educational or other reasons, more than one access may occur in relation to a single patient or, conversely, health professionals may manage patients without reference to TOXBASE®. The NPIS telephone call data are case specific, but enquiries are made for only a minority of cases that present, for example, when there are particular clinical concerns, when TOXBASE® is not available or the information provided there is not sufficient, and may not include complications experienced after the telephone enquiry, because follow-up data are incomplete. These data therefore provide only an indirect reflection of the frequency with which health professionals encounter cases of toxicity and most probably underestimate the incidence of quinine toxicity. Although national data on annual numbers of admissions are available via Hospital Episode Statistics, this does not provide specific data on admissions with quinine poisoning but only aggregated data for all antimalarial drugs.

Mitigation of the toxic effects from pharmaceutical poisoning has become an increasingly important role for regulatory authorities. The European Union Directive 2010/84/EU [12] now obliges member states to operate pharmacovigilance systems that collect information on toxicity arising from overdose as well as normal therapeutic use. There is evidence that this approach can inform regulatory actions which result in reduced risk of overdose and subsequent morbidity [13]. The evidence presented in the present study suggests that the MHRA drug safety update

has reduced quinine prescribing, but the effect appears to have been limited and not sustained. This might be expected, because this was a single publication available on the MHRA website and via an email circulation which, although distributed to more than 200 000 email addresses, does not reach all UK prescribers. The modest impact observed is consistent with the limited effects on prescribing and self-harm of MHRA advice on prescribing of selective serotonin reuptake inhibitor antidepressants to children and adolescents issued in 2003 [14].

Larger changes in prescribing might occur after use of more direct methods of communication with a wider circulation, such as a 'Dear Health Professional' letter. Specific changes to drug licences, however, may be needed in order to have a more substantial effect on prescribing with measurable benefits to public health. For example, reductions in prescribing and episodes of overdose followed restrictions to the indications for thioridazine in 2000 [15]. As would be expected, substantial impact was demonstrated following the withdrawal of the licence for co-proxamol in 2005, a preparation similar to quinine in terms of limited efficacy and profound toxicity in overdose. This resulted in a reduction in overall mortality from drug poisoning [16]. In any event, it would seem important for the MHRA to assess and publish the impact of their interventions. Although some pharmacoepidemiology work is carried out by the MHRA to follow up on some of its safety alerts, this is not universally applied and could usefully be extended.

Prescribers and commissioners of health care also have a responsibility to take appropriate action in response to drug safety advice. The profound differences in response to the MHRA update between PCTs demonstrate a variable commitment between organizations to adopt drug safety advice. The striking reduction in quinine prescribing achieved by PCT 'D' followed a comprehensive review of current users of quinine aimed at removing quinine from repeat prescriptions and encouraging the use of safer alternative treatment modalities. We would expect similar measures, adopted nationally, to achieve substantial reductions in quinine prescribing, with consequent reduction in the incidence of severe toxicity following quinine overdose or after therapeutic use. It seems likely, however, that universal and consistent adoption of such measures would need specific direction from organizations with a responsibility for quality of care, such as the Care Quality Commission or the Department of Health's Quality, Innovation, Productivity and Prevention programme.

Conclusions

The MHRA drug safety update has had a limited effect on quinine prescribing and indices of toxicity, with more substantial reductions in quinine prescribing being achieved in areas where comprehensive local measures were adopted. Quinine prescribing, however, remains common,

and further steps are needed to discourage inappropriate prescribing and thus the risk of toxicity after therapeutic dosing or overdose.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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