

Antipyretic drug use in children in French office based medical practice[†]

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SUMMARY

Purpose To analyse antipyretics (APs) prescriptions profile in children, particularly the frequency of AP combinations.

Methods APs (acetylsalicylic acid, paracetamol, ibuprofen or ketoprofen) prescribed to children below 12 years and refunded by a public health insurer in 2003, throughout France, were examined.

Results A total of 513 034 prescriptions were refunded for 240 720 children. The mean number of AP prescriptions per child was the highest in children aged 6 months to 2 years. Paracetamol was the main AP prescribed, but its prescription declined with age, from 90.8% below 3 months old to 57.4% between 6 and 12 years old. Ibuprofen-only prescriptions were rare below 3 months and maximal between 2 and 6 years. The ibuprofen/paracetamol combination was prescribed from 6 months old, and its frequency was maximal between 2 and 6 years old (21.7%).

Conclusions The clear predominance of paracetamol prescriptions suggests that French prescribers are relatively aware of the relative risk-benefit ratio of the different APs. Studies are required to determine if the APs are prescribed to be used alternately or when a monotherapy fails. Guidelines to manage fever in children are needed in France to restrict APs combination to the case of paracetamol failure. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS—antipyretic; children; prescription; antipyretic combination; paracetamol; ibuprofen

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INTRODUCTION

Four drugs are approved in France to treat fever in children, namely paracetamol and three nonsteroidal anti-inflammatory drugs (NSAIDs), i.e. aspirin, ibuprofen and ketoprofen.¹

In 1980s, the dose regimen in the French marketing terms for paediatric paracetamol preparations was

30 mg/kg/d. This dose was inadequate, and a second antipyretic (AP), generally aspirin, was therefore frequently required. This practice of combining two APs persisted in France even though in 1995, the French Drug Agency approved a higher dose of paracetamol, from 30 to 60 mg/kg/d, and up to 80 mg/kg/d. However, no data have shown the benefit of this combination of two APs prescribed in adequate dosage.^{2–5} Paediatric ibuprofen, marketed in 1993 for fever, gradually replaced aspirin alone or in combination with paracetamol. French guidelines for fever management in children were lacking at the beginning of this study.

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OBJECTIVE

The aim of this study was to analyse APs prescriptions profile in children below 12 years in French office based medical practice.

METHODS

The source data were refunded prescriptions by the Caisse Nationale d'Assurance Maladie—Assurance Maladie des Professions Indépendantes (CANAM—AMPI) health insurer. This health insurance system is obligatory for shopkeepers and artisans, and caters to the needs of nearly three million people (policyholders and their dependants). From the source data we retrieved and analysed the profile of prescriptions to children between January 2003 and December 2003 based on the four drugs, i.e. acetylsalicylic acid, paracetamol, ibuprofen and ketoprofen, approved to treat fever in children. In all French systems of health insurance, prescriber's name and quality, child's name and age, date of prescription and drugs prescribed (dosage and length) are recorded disregarding the drug indication.

The mean number of prescriptions was compared according to the age group (0–3 months, 3–6 months, 6 months to 2 years, 2–6 years and 6–12 years). Since age groups were not of equal range, we therefore estimated the mean number of prescriptions during one trimester (the smallest age group) within each age group.

RESULTS

Global analysis

A total of 513 034 APs were refunded for 240 720 children. The proportion of children prescribed at least one AP increased with age to be maximal in the 6–24-month olds (79%), which gradually decreased (Table 1). Using the trimester as the time measure, the mean number of AP prescriptions increased with age to be maximal in the 6–24-month olds (0.48), which subsequently declined with increasing age, to be the same among children aged 0–3 months than among children over 6 years.

Distribution of antipyretics by age group

Distribution of APs varied according to the age (Figure 1). Paracetamol, alone or in combination, was the main AP prescribed to all age groups especially for the 0–3-month olds (96.9% of APs) and for the 3–6-month olds (93.6% of APs). This predominance of paracetamol alone or in combination became less pronounced with increasing age (86.8, 80.2 and 78.1%, respectively, in the 6-month to 2-year olds, 2–6-year olds and 6–12-year olds). Conversely, prescriptions of ibuprofen, alone or in combination, increased with age, intentionally being higher in the over-6 months than in younger children: 32.2, 38.7 and 30.9%, respectively, in the 6-month to 2-year olds, 2–6-year olds and 6–12-year olds.

The proportion of paracetamol-only prescriptions declined with age, from 90.76% below 3 months to

Table 1. Antipyretic (AP) prescriptions by private practitioners to children below 12 years, in 2003

Age group	Children insured	Children with at least one AP prescription (%)	AP prescriptions* (%)	Mean number of prescriptions per age group [†] (%)	Mean number of prescriptions per trimester, by age group [‡]
0–3 months	10 479	5342 (51.0)	6602 (1.3)	0.22	0.22
3–6 months	13 880	8202 (59.1)	13 048 (2.5)	0.43	0.43
6 months–2 years	37 385	29 519 (79.0)	88 307 (17.2)	2.90	0.48
2–6 years	105 551	78 029 (73.9)	185 007 (36.1)	6.07	0.38
6–12 years	198 341	119 628 (60.3)	220 070 (42.9)	7.22	0.20
Total	365 636	240 720 (65.8)	513 034 (100.0)	16.80	

*Percentage of the 513 034 prescriptions in each age group.

[†]The mean number of prescription was calculated as follows: (1) 513 034 prescriptions were observed during the 1-year study period in a sample of 365 636 children, i.e. a mean of 1.40 prescriptions per child per year; (2) during the first 12 years of life, a typical child therefore receives an average of 16.8 prescriptions (12×1.40); (3) an estimated 1.3% of prescriptions were made to children below 3 months, and 2.5% to children aged 3–6 months. Assuming that the 16.80 prescriptions received by the average child between 0 and 12 years old follow the same distribution, on average a child will receive 0.22 prescriptions between 0 and 3 months old ($16.80 \times 1.3\%$), 0.43 between 3 and 6 months old ($16.80 \times 2.5\%$) and 2.90 between 6 months and 2 years old ($16.80 \times 17.2\%$).

[‡]The value for the 6-month to 2-year olds was obtained by dividing 2.90 by 6 (the number of trimesters between 6 months and 2 years) and is interpreted as follows: a typical child, between 6 months and 2 years old, receives an average of 0.48 prescriptions each trimester. The same principle was applied to the other age group.

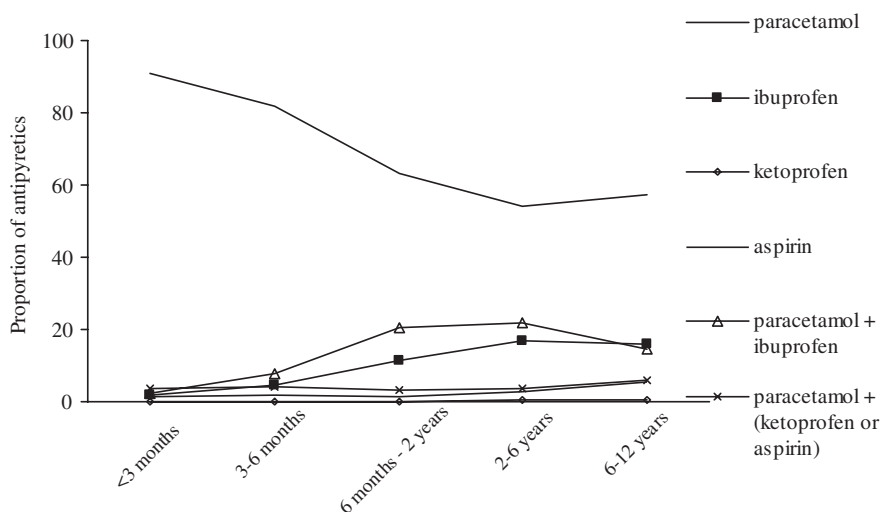


Figure 1. Distribution of antipyretic prescriptions according to age

57.39% between 6 and 12 years. The proportion of ibuprofen-only prescriptions (licensed from 3 months upwards in France) was low below 3 months (1.6%) and maximal between 2 and 6 years (16.7%). The proportion of ketoprofen-only prescriptions (authorised from 6 months upwards) did not exceed 0.5% in any age group. The proportion of aspirin-only prescriptions increased gradually with age, and was maximal between 6 and 12 years (5.5%).

The ibuprofen/paracetamol combination was exceptional below 6 months and the highest between 2 and 6 years (21.7%). Combination of two or more NSAIDs, including aspirin, increased gradually with age but remained rare ($\leq 0.4\%$).

Analysis according to the region

Distribution of prescriptions for the different APs and their combinations were similar throughout the five French regions, Northwest, Northeast, Southwest, Southeast and Paris region (Figure 2).

Analysis according to the prescriber

AP prescriptions were equally distributed between general practitioners and paediatricians among children below 3 months. In contrast, proportion of prescriptions done by general practitioners increased with age. Overall, the paediatricians were more inclined to prescribe paracetamol monotherapy, and rather fewer NSAIDs, and fewer paracetamol/NSAID combinations than general practitioners (Figure 3).

DISCUSSION

The predominance of APs prescription between 6 months and 2 years olds was due to the high frequency of febrile viral infections and the risk of febrile convulsions in this age group. Contrarily, the low frequency of febrile disorders in children below 3 months was reflective due to less AP prescriptions in this age group.

Paracetamol was the unique AP prescribed in children below 3 months, which is in accordance with the licence terms of APs, as paracetamol is the unique AP authorised from birth.

The clear predominance of paracetamol regardless of age despite a lack of French guidelines was in accordance with its higher safety than NSAIDs, which are associated with cutaneous, digestive and renal side effects.⁶⁻⁸

Although the data collection method does not allow to distinguish co-prescribed APs intended for systematic combination therapy from a combination to rely on only when monotherapy failed, the frequency of APs combination, particularly paracetamol/ibuprofen (about 20% of all APs prescriptions), is surprising. In fact, systematic AP combination is illogical⁹ first of all because monotherapy is most often effective at the approved dose; the second reason is no data assessed effectiveness of such APs combination while the risk of adverse effects is cumulative. Moreover, if serious adverse effects occur during APs combination, both drugs would be contraindicated, depriving young children of two of the most crucial labelled drugs for a frequent and recurrent disease.

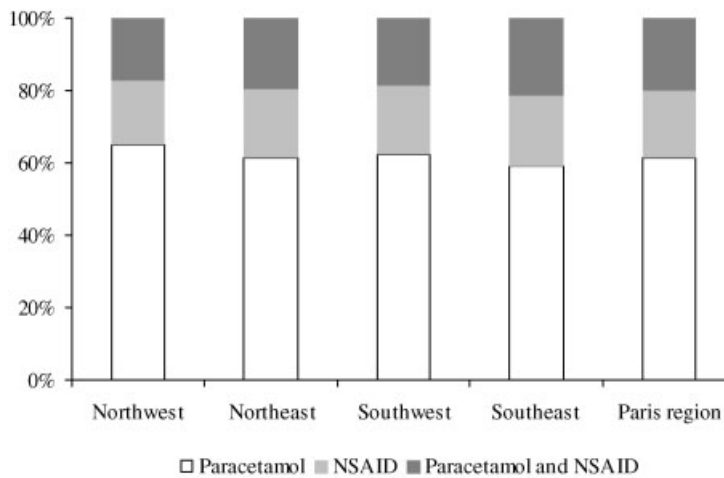


Figure 2. Distribution of antipyretic prescriptions according to the region

The homogeneous distribution of the different APs and their combinations in the regions studied here reflected a general consensus throughout France. It suggested that regional opinion leaders did not have major influence in this respect.

Our descriptive study of APs prescription profile in France had some limitations. First, as indication of drugs refunded was unknown, so it was difficult to distinguish drugs prescribed for fever from those for pain. A second limitation was the fact that there was no compliance with prescription and self-medicated

APs. Third, our study method did not allow to distinguish co-prescribed APs intended for systematic combination therapy in the case when initial monotherapy failed. Finally, children catered by the AMPI health insurer may not be representative of general French paediatric population. We had no specific data on this matter, but refundable prescriptions to children were probably independent of the parents' profession.

One study took into consideration the evolution of APs use in children in France between 1981 and 1992.¹⁰ Overall, the proportion of children exposed to

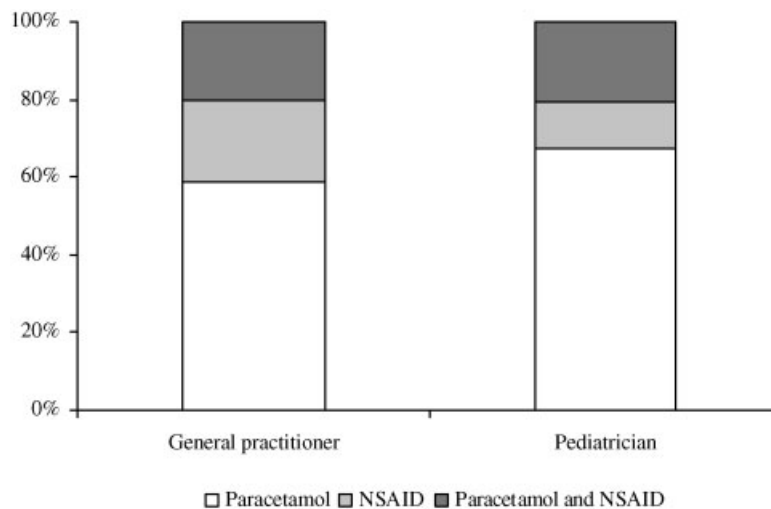


Figure 3. Distribution of antipyretic prescriptions according to prescriber

APs increased significantly (+28%) between 1981 and 1992. Among them, percentage of children treated with aspirin decreased (-27%), while it increased for paracetamol (+19%) and for NSAIDs (+179%). Aspirin was the most used AP in 1981 (57%). However, it was replaced by paracetamol in 1992 (72%). On the other hand, the ibuprofen prescriptions gradually arose. Ibuprofen replaced aspirin because of the risk of Reye's syndrome, a very rare but very severe disease which has been observed in children with viral illnesses (particularly chickenpox or flu symptoms) receiving aspirin.^{11,12} In France summary product characteristics of pediatric forms of aspirin includes warnings and precaution: 'Aspirin containing preparations should not be given to children unless on the advice of a doctor and if other treatment failed'. In UK the Committee on Safety of Medicines has given Warnings and Precautions: 'Do not give to children aged below 16 years, unless on the advice of a doctor and unless specifically indicated (e.g. for Kawasaki's disease)'. In North America, the food and drug administration has given a contraindication: 'aspirin should not be used in children or teenagers for viral infections, with or without fever'. Ketoprofen, despite being authorised in France since 1999 to treat fever from 6 months upwards, is rarely prescribed, because it has never been promoted by the firm whatever the age group may be.

If one agrees that monotherapy is preferable and that paracetamol is the first-line treatment to manage fever in children, our results suggest that most French practitioners prescribe APs rationally (paediatricians a little better than general practitioners). However, there is still room for improvement, notably by reducing the frequency of AP combinations, which must be reserved in case of monotherapy failure (persistence of fever despite an adequate unit dose given at fixed intervals). Paracetamol monotherapy should remain the first-line therapy because of its comparable AP efficacy and its better safety profile than ibuprofen.⁷ Ibuprofen inhibits prostaglandin biosynthesis as all NSAIDs, and can induce digestive bleeding and renal failure even in children. In clinical trials in febrile children,²⁻⁵ the frequency of adverse effects, especially gastrointestinal effects, was higher with ibuprofen 20-30 mg/kg/d than with paracetamol or placebo, even if the differences were not significant, owing to a lack of statistical power.¹³ In a very large double-blind trial involving 84 182 febrile children in which paracetamol (12 mg/kg) was compared with ibuprofen (5 or 10 mg/kg), four cases of gastrointestinal bleeding occurred in the ibuprofen groups within 4 weeks of treatment outset (two cases with 5 mg/kg and two

cases with 10 mg/kg), giving a risk of gastrointestinal bleeding of 7.2/100 000 (95%CI 2-18/100 000).⁶ The risk of renal failure associated with NSAIDs is probably very low with ibuprofen but it increases in situations with volume depletion. Ulinski and Bensman¹⁴ reported series of children presenting with febrile diarrhoea who were treated with therapeutic doses of ibuprofen before developing acute renal failure. Moreover, a significant association between ibuprofen and necrotising fasciitis during chickenpox was shown in a case control study.⁸

CONCLUSION

Paracetamol was the most widely prescribed AP by French practitioners, but its combination with ibuprofen represented about 20% of all AP prescriptions. Further studies are required to determine the conditions in which APs combination was prescribed. Guidelines to manage fever in children, which were lacking in France at the beginning of the study, were published in 2005. They are in accordance with our conclusion that a monotherapy is the first-line treatment of fever and, because of its benefit risk, balance paracetamol is the best choice in children.

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