

Acetylsalicylic-acid-containing drugs and nonsteroidal anti-inflammatory drugs available in Canada

Malcolm Brigden, MD, CM; Reginald E. Smith, PharmD

Abstract

A LARGE NUMBER OF DRUGS containing acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) are available by prescription and over the counter in Canada. The possibility of serious side effects and drug interactions is therefore high. The authors have compiled a comprehensive list of products containing these drugs from information supplied by pharmaceutical databases, independent marketing researchers and Health Canada's Drug Directorate. Physicians should ensure that additional ASA-containing drugs or NSAIDs are not inadvertently taken by patients, especially those receiving oral anticoagulant therapy or those with a qualitative platelet defect. Patients at risk should be cautioned to check with their physician before taking any new medication, even over-the-counter products.

Résumé

DE NOMBREUX MÉDICAMENTS contenant de l'acide acétylsalicylique (ASA) et des anti-inflammatoires non stéroïdiens (AINS) sont disponibles sur ordonnance et en vente libre au Canada. Le risque d'effets secondaires graves et d'interactions entre médicaments est donc élevé. Les auteurs ont dressé une liste détaillée des produits qui contiennent ces médicaments à partir de renseignements provenant de bases de données pharmaceutiques, de chercheurs indépendants en marketing et de la Direction des médicaments de Santé Canada. Les médecins devraient s'assurer que leurs patients ne prennent pas par inadvertance d'autres médicaments contenant de l'ASA ou des AINS, surtout dans le cas des personnes qui prennent des anticoagulants par voie orale ou qui ont un défaut plaquettaire qualitatif. Il faudrait prévenir les patients à risque de consulter leur médecin avant de prendre de nouveaux médicaments, même en vente libre.

Drugs containing acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely available and frequently prescribed. The possibility of serious side effects and drug interactions is therefore high. Physicians need to ensure that additional ASA-containing drugs or NSAIDs are not inadvertently taken, especially by patients receiving oral anticoagulant therapy or those with a qualitative platelet defect such as that associated with von Willebrand's disease, uremia, dysproteinemia or a myeloproliferative disorder.

Although a variety of population-based surveys of ASA awareness and utilization have been performed, most antedated the widespread publicity surrounding primary and secondary prevention trials.¹⁻³ One recent survey of a Canadian community found that 8% of 666 respondents took ASA routinely.⁴ Among those over the age of 50 (who would be more likely to receive concomitant oral anticoagulant therapy) the figures rose to 19% of men and 14% of women. In addition, there is evidence that NSAIDs are used more frequently than physicians suspect.⁵⁻⁷ Furthermore, regular NSAID users are as likely to use ASA as non-NSAID users, despite the dubious additional analgesic benefit.⁸ We hope that the provision of up-to-date information on the availability of ASA-containing drugs and NSAIDs will help inform physicians as to the magnitude of this problem.

No single database of ASA-containing drugs and NSAIDs is readily available in Canada. Therefore, we created a comprehensive list by examining information



Education

Éducation

Dr. Brigden is Regional Medical Oncologist, Penticton Regional Hospital, Penticton, BC, and Dr. Smith is with the Pharmacy Department, Division of Cardiology and Cardiovascular Surgery, Royal Jubilee Hospital, Victoria, BC.

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from pharmaceutical databases, independent marketing researchers and Health Canada's Drug Directorate. The lists of products were extensively cross-checked against information in Health Canada's database. The ASA-containing product list was generated by searching the Health Canada database for any registered human drug product with ASA as an ingredient. The NSAID list was generated by searching the same database for human drugs that had American Hospital Formulary Service therapeutic classification 28:08.04 (nonsteroidal anti-inflammatory agent).

We were able to identify over 130 ASA-containing medications (Table 1) and 27 NSAIDs (Table 2) from the Health Canada database. Although many of the ASA-containing drugs identify ASA in the product name, many do not.

Drug mechanisms and interactions

When patients receive oral anticoagulant therapy the addition of a qualitative platelet defect may increase the risk of hemorrhage. Several investigators have evaluated

the clinical efficacy of combining anticoagulants with antiplatelet drugs, especially ASA.⁹⁻¹⁵ Although results from these trials are difficult to compare because of differing target INRs (international normalized ratios) and ASA dosages, every trial demonstrated an increased incidence of hemorrhage, even with ASA dosages as low as 100 mg/d. Fortunately, major hemorrhage has occurred mainly with high-dose ASA therapy; low-dose ASA therapy has been associated more often with an increased risk of minor hemorrhage and only a slightly increased risk of major hemorrhage.¹⁰⁻¹⁵

ASA inactivates cyclooxygenase, therefore decreasing the production of prostaglandins.¹⁶⁻¹⁸ Although the lowest possible dose of ASA that will induce a qualitative platelet defect is not precisely known, a single oral dose of 5 to 100 mg has been shown to produce dose-dependent inhibition of platelet cyclooxygenase activity, with 100 mg almost completely suppressing the biosynthesis of thromboxane A₂ in healthy subjects.¹⁸ This inhibitory effect is rapid and occurs before the drug appears in the systemic circulation, probably because of the acetylation of platelet prostaglandin synthase in the portal circulation. Thus, the

Table 1: Products containing acetylsalicylic acid (ASA) available in Canada*

| | | | |
|---|--|---|--|
| Over the counter | Stanley Pharmaceuticals, Wampole, WestCan) | Calmine (Les Lab Vachon) | Robaxisal-C% (Whitehall-Robins) |
| A.C.&C. (Clark Labs, Pharmascience, Stanley Pharmaceuticals, Wampole, WestCan) | ASA ECT (Bionatal, Drug Trading, Pharmaprix, Shoppers Drug Mart) | Centra ASA boluses (Central) | Tri-Buffered ASA (Zee Medical) |
| AC with Codeine (Drug Trading) | A.S.A. Enteric Coated (WestCan) | Coated Aspirin (Bayer) | 217 (Johnson & Johnson) |
| Acetylsalicylic Acid (Drug Trading, Gen Drug, Pharmascience, Pharmel) | ASA Suppositories (Pharmascience) | Coricidin (Schering Canada) | 217 Strong (Johnson & Johnson) |
| Acetylsalicylic Acid Boluses (Langford) | Asaphen (Pharmascience) | Coricidin "D" (Schering Canada) | 222 (Johnson & Johnson) |
| Acetylsalicylic Acid Boluses (Gen Drug) | Aser Powder (Jaapharm) | Coricidin "MD" (Schering Canada) | Upsarin Effervescent (UPSA Can) |
| Acetylsalicylic Acid with caffeine and codeine phosphate (Stanley Pharmaceuticals) | Aspergum Cherry/Orange (Schering-Plough) | Coryphen (Rougier) | Upsarin Effervescent Extra Fort (UPSA Can) |
| Alka-Seltzer (Bayer) | Aspirin (Bayer) | Cunnard Casse Grippe Cap | |
| Alka-Seltzer Flavored (Bayer) | Aspirin Bolus (Med:Biotech) | Dolomine 37 (Frega) | |
| Alka-Seltzer Plus Cold Medicine (Bayer) | Aspirin Chewable (Bayer) | Dristan Capsules (Whitehall-Robins) | Prescription |
| Anacin (Whitehall-Robins) | Aspirin Children's (Bayer) | Dry Socket Paste (Sultam Chemists) | AC with Codeine (Drug Trading) |
| Anacin with Codeine (Whitehall-Robins) | Aspirin, Coated (Bayer) | Entrophen, all formulations (Johnson & Johnson) | Asasantine (Boehringer Ingelheim) |
| Anacin Extra Strength (Whitehall-Robins) | Aspirin Enteric Coated (Bayer) | Equagesic (Wyeth-Ayerst) | Coryphen Codeine (Rougier) |
| Antidol (Produits Gerbex) | Aspirin Extra Strength (Bayer) | Headache Tablets (Romilo Labs) | Darvon-N products (Eli Lilly) |
| Apo-ASA (Apotex) | Aspirin Plus Stomach Guard (Bayer) | Herbopyrine (Herbes Universelles) | Endodan (Endo) |
| Arco Pain (Romilo Labs) | Aspirin Plus Stomach Guard Extra Strength (Bayer) | Instantine (Bayer) | Fiorinal (Sandoz Canada) |
| ASA (Adams Labs, Drug Trading, Everest Pharmaceuticals, Novopharm, Pharmaprix, Pro Doc Lab, Shoppers Drug Mart, | Astone (Ramelco) | Kalmex (Rolmex) | Fiorinal-C (Sandoz Canada) |
| | Astrin (Medic Laboratory) | Madelon (Romilo Labs) | Novo-Propoxyn Compound (Novopharm) |
| | Bexton Pwr (Bexco Pharm) | MED Tigol (Hilary's Distribution) | Oxycodan (Technilab) |
| | Bufferin (Bristol-Myers Squibb) | Midol (Bayer) | Painex (ICN Canada) |
| | Bufferin Extra-Strength (Bristol-Myers Squibb) | MSD Enteric Coated ASA (Merck Sharp & Dohme) | Percodan (Du Pont Pharma) |
| | CT Acetylsalicylic acid codeine & caffeine (Pharmasave Lab) | Nervine (J.L. Mathieu) | Percodan-Demi (Du Pont Pharma) |
| | C2 Buffered (Wampole) | Nezger (Produits Gerbex) | Phenaphen No. 2, No. 3, No. 4 (Wyeth-Ayerst) |
| | C2 Buffered with Codeine (Wampole) | Norgesic (3M Pharmaceuticals) | Robaxisal-C¼, C½ (Whitehall-Robins) |
| | C2 with Codeine (Wampole) | Norgesic Forte (3M Pharmaceuticals) | 692 (Frosst) |
| | | Novasen Sp.C. (Novopharm) | Tecnal (Technilab) |
| | | Novo A C & C (Novopharm) | Tecnal C¼, C½ (Technilab) |
| | | Pain Aid (Zee Medical) | 282 (Frosst) |
| | | Robaxisal (Whitehall-Robins) | 282 Mep (Frosst) |
| | | | 292 (Frosst) |



antiplatelet effect of ASA is not necessarily related to its systemic bioavailability.¹⁸

Because platelets lack a nucleus and cannot synthesize new proteins, the qualitative defect induced by ASA lasts the platelet's life span (approximately 8 to 10 days). After the last dose of ASA has been administered, there is little or no recovery of platelet cyclooxygenase activity for 2 to 3 days.

Whereas ASA acetylates the platelet membrane for the duration of the platelet's life span, NSAIDs are reversible

inhibitors of platelet cyclooxygenase activity and hence prostaglandin synthesis.¹⁹⁻²² Several studies have shown that, as with ASA use, the administration of NSAIDs can increase postoperative blood loss.²³⁻²⁶ However, careful studies attempting to correlate the degree of NSAID-induced inhibition of prostaglandin synthesis, anti-inflammatory efficacy and the associated degree of qualitative platelet defect induced by individual agents are reportedly not available.^{26,27}

Table 2: Nonsteroidal anti-inflammatory drugs other than ASA available in Canada

| Generic name | Common trade names |
|---|---|
| Cimicifuga | Artrol |
| Choline salicylate-magnesium salicylate | Trilisate |
| Diclofenac sodium | Apo-Diclo, Apo-Diclo SR, Arthrotec, Diclofenac Ect, Novo-Difenac, Novo-Difenac SR, Nu-Diclo, Taro-Diclofenac, Voltaren, Voltaren SR |
| Diclofenac potassium | Voltaren Rapide |
| Diflunisal | Apo-Diflunisal, Dolobid, Novo-Diflunisal, Nu-Diflunisal |
| Etodolac | Ultradol |
| Fenoprofen calcium | Nalfon |
| Floctafenine | Idarac |
| Flurbiprofen | Ansaid, Apo-Flurbiprofen FC, Froben, Froben SR, Novo-Flurprofen, Nu-Flurbiprofen |
| Ibuprofen | Actiprofen, Advil, Advil Cold & Sinus, Amersol, Apo-Ibuprofen, Excedrin IB, Medipren, Motrin, Motrin IB, Novo-Profen, Nuprin, Nu-Ibuprofen, Sinus Pr & Pain Reliever with Ibuprofen |
| Indomethacin | Apo-Indomethacin, Indocid, Indocid SR, Indolec, Novo-Methacin, Nu-Indo, Pro-Indo, Rhodacine |
| Ketoprofen | Apo-Keto, Apo-Keto-E, Novo-Keto, Novo-Keto-Ec, Nu-Ketoprofen, Nu-Ketoprofen-E, Orudis, Orudis E, Orudis SR, Oruvail, PMS-Ketoprofen, PMS-Ketoprofen-E, Rhodis, Rhodis-EC |
| Ketorolac tromethamine | Acular, Toradol |
| Magnesium salicylate | Back-Ese-M, Doan's Backache Pills, Herbogesic |
| Mefenamic acid | Ponstan |
| Nabumetone | Relafen |
| Naproxen | Apo-Naproxen, Naprosyn, Naprosyn-E, Naxen, Novo-Naprox, Nu-Naprox, PMS-Naproxen |
| Naproxen sodium | Anaprox, Anaprox DS, Apo-Napro-Na, Naproxin-Na, Novo-Naprox Sodium, Synflex, Synflex DS |
| Oxyphenbutazone | Oxybutazone |
| Phenylbutazone | Alka Phenyl, Alka Phenylbutazone, Apo-Phenylbutazone, Butazolidin, Novo-Butazone, Phenylone Plus |
| Piroxicam | Apo-Piroxicam, Feldene, Kenral-Piroxicam, Novo-Pirocam, Nu-Pirox, PMS-Piroxicam, Pro-Piroxicam, Rho-Piroxicam |
| Salsalate | Disalcid |
| Sodium salicylate | Dodd's, Dodd's Extra-Strength |
| Sulindac | Apo-Sulin, Clinoril, Novo-Sundac, Nu-Sulindac, Sulindac |
| Tenoxicam | Mobiflex |
| Tiaprofenic acid | Albert Tiafen, Apo-Tiaprofenic, Surgam, Surgam SR |
| Tolmetin sodium | Novo-Tolmetin, Tolectin |



NSAIDs may interact with warfarin through a number of mechanisms.^{27,28} Some NSAIDs may be less likely to interact with coumarin anticoagulants; however, the available information is conflicting.²⁷⁻³⁰ It is beyond the scope of this paper to quantify the degree of risk for each drug.

Conclusion

The large number of ASA-containing drugs and NSAIDs available in Canada make it necessary for physicians to ensure that patients requiring oral anticoagulant therapy do not acquire a superimposed qualitative platelet defect. A list of ASA-containing drugs and NSAIDs should be reviewed with all patients beginning oral anticoagulant therapy and with those who have a qualitative platelet defect such as that associated with von Willebrand's disease, uremia, dysproteinemia or a myeloproliferative disorder. The patients should be cautioned to check with their physicians always before taking any new medication, including over-the-counter preparations.

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Reprint requests to: Dr. Malcolm Brigden, Regional Medical Oncologist, Penticton Regional Hospital, 550 Cami Ave., Penticton BC V2A 3G6; fax 250 492-9036

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