Barriers in the quest for quality drug information: salutary lessons from TGA-approved sources for thyroid-related medications

Jim R Stockigt

ABSTRACT

- Product information (PI) for thyroid-related medications endorsed by the Therapeutic Goods Administration, as reproduced in the commonly used compilation publications *June 2006 MIMS (Monthly index of medical specialties) annual*, MIMS Online and the *Australian prescription products guide 2006*, was evaluated to see whether it reflects contemporary therapeutic practice.
- Compared with current medical literature, these PI-based sources provide inadequate, inaccurate or outdated therapeutic directives. Examples include:
  - Incorrect advice that thyroxine therapy should *always* begin at very low dosage.
  - Failure to recommend increased thyroxine dosage *early* in pregnancy (thus placing the offspring of women being treated for hypothyroidism at risk of impaired fetal brain development).
  - Incorrect and potentially unsafe advice to treat thyrotoxicosis with stable iodide in late pregnancy.
  - Failure to advise serial adjustment of antithyroid drug dosage until *after* a patient becomes euthyroid (this can result in iatrogenic thyroid dysfunction).
  - Outdated advice that antithyroid drugs are not compatible with breastfeeding.
- Recent initiatives to upgrade consumer medicine information (CMI) appear to accept PI-based sources as a reliable benchmark for CMI. That inference is not warranted for thyroid-related medications.
- Accountability for the updating of clinical information in PI needs to be defined, and the process for updating PI may need to be modified.
- Quality drug information, both PI and CMI, depends on fluent, evidence-based collaboration between suppliers, regulators, prescribers, specialist clinicians and consumers.

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In iodine-replete countries, about 5% of the population have a thyroid disorder,[1] of whom about a quarter will require long-term medication either to correct deficiency or to control thyroid hormone excess. In 2005, about 700 000 Pharmaceutical Benefits Scheme prescriptions were filled in Australia for thyroxine, with about 80 000 scripts for the antithyroid drugs carbimazole and propylthiouracil.[2]

Although no major new therapeutic agent has been introduced in the thyroid field for some years, the body of knowledge and evidence has advanced. It is important that these developments are reflected in the product information (PI) widely used by medical practitioners and a range of health professionals, who may not refer directly to current scientific literature on thyroid disorders. *MIMS (Monthly index of medical specialties) annual*,[3] in its 30th edition in 2006, and the *Australian prescription products guide (APPG) 2006*, 35th edition,[4] are the most commonly used compilations of PI (provided by the drug manufacturer and approved by the Therapeutic Goods Administration [TGA]). Both are mandatory pharmacy references specified by some state pharmacy boards.[5,6]

My review assesses whether PI-based information on thyroid-related medications as reproduced in *MIMS annual* 2006, MIMS Online and *APPG 2006* is in accord with current peer-reviewed medical literature and contemporary therapeutic practice.

Importance of thyroid-related drug information

There are several reasons why patients taking thyroid-related medications, who number over 200 000 in Australia, need reliable information. First, they should aim for some self-sufficiency in relation to their medications, because long-term treatment and follow-up often extends beyond contact with any one medical practitioner. Second, they may need to make informed choices between therapeutic alternatives. For example, a young woman with thyrotoxicosis who has future plans for pregnancy may be offered ablative treatment, with the prospect of subsequent lifelong thyroxine replacement therapy that will need to be adjusted during pregnancy. Her alternative of antithyroid drug treatment, with the possibility of remission or recurrence, might be dismissed if she were given poorly documented advice about the safety of antithyroid drugs during pregnancy and lactation. Third, there is potential for ill-advised dose adjustment, failure to recognise side effects and, at times, misuse[7] of thyroid-related drugs.

Sources of drug information

The stated aim of the 2006 *MIMS annual* is to serve as "the byword for accurate, reliable, comprehensive and independent medicines information". It also states that "Prescribers, and health care professionals in general, need to be confident in today's litigation-conscious environment that the information used as decision support, in both electronic and print formats, is reliable, accurate, from a trusted source AND reflects the current APPROVED information".[3] Further, the title page of the 2006 *MIMS annual* states that "Product monographs in MIMS annual represent Therapeutic Goods Administration (TGA) approved product information, which is the result of years of research and development by the sponsor company and of painstaking evaluation and review by the Drug Safety and Evaluation Branch of the TGA".[3] These statements imply an intention to offer both pharmaceutical information and reliable clinical advice. It follows that patient care can be influenced by the quality and accuracy of the information in PI supplied by pharmaceutical manufacturers or sponsors, and then endorsed by the TGA. This potential link to clinical decisions mandates accountability for PI-based drug information.

Contentious, unsafe, omitted or undocumented recommendations for thyroid-related medications, as reproduced in *MIMS* and *APPG* from approved product information (my emphasis indicated by italics)

THYROXINE

Initiation of therapy

"*In all cases*, Oroxine [Sigma] should be initiated at not more than 50 microgram/day and gradually increased …"

Critique: This absolute restriction, based on caution in initiating thyroxine therapy in elderly patients with hypothyroidism, may be quite inappropriate. After near-total thyroidectomy in a euthyroid healthy adult, full replacement dosage should be used[8-10,13] to avoid unnecessary iatrogenic hypothyroidism. For newly diagnosed hypothyroidism in pregnancy, 1.5–2.0 µg/kg per day is now recommended as the initial dosage.[14]

Quality of evidence: Reference 8-10 (III-2, B); 13 (IV, B); 14 (III-3, B).

Dose modification in pregnancy

"For women with established hypothyroidism, thyroxine replacement generally needs to be increased by 25 to 40% during pregnancy, based on measurements of TSH and thyroxine levels *at the end of the first and second trimesters*."

Critique: Dosage does need to be increased, particularly to avoid any degree of hypothyroidism in the first trimester, when fetal brain development is critically dependent on maternal thyroxine.[15] Adjustments based on measurements at the end of the first trimester are likely to be too late to address this need.[14] Contemporary advice is to optimise the dose of thyroxine when pregnancy is anticipated, and to increase dosage by about 30% when pregnancy is confirmed.[14] In addition, the statement "clinical experience does not indicate any adverse effects on the foetus when the thyroid agents are administered during pregnancy" would be more pertinent if it emphasised the need to increase dosage early in pregnancy to avoid the adverse effect on the fetus of under-replacement.[14,15]

Quality of evidence: Reference 14 (III-3, B); 15 (III-2, B).

Indications incompletely documented

Further indications for the use of thyroxine that have been omitted are:
1. Thyroxine may be used in conjunction with an antithyroid drug (block–replace regimen) for the management of thyrotoxicosis.[8,16]

2. Thyroxine may be used in euthyroid goitre, especially before nodularity has developed, aimed at inhibiting goitre growth by suppressing TSH.[17]

Quality of evidence: Reference 8, 16, 17 (III-3, B).

CARBIMAZOLE

Thyrotoxicosis in pregnancy

"Neo-Mercazole [Link] should be discontinued three to four weeks before delivery *and a course of iodine should be substituted.*"

Critique: This recommendation is not based on any evidence and is contrary to current practice. Substitution of stable iodide for an antithyroid drug late in pregnancy can be a serious error and is contraindicated. Excess iodide can cause fetal goitre and neonatal hypothyroidism, especially in premature infants.[18,19] High-dose iodide should not be given in pregnancy, except, when necessary, as preparation for surgery.[19] If required, carbimazole can be safely continued, at the lowest possible dose.

Quality of evidence: Reference 18, 19 (IV, B).

Breastfeeding

"*Infants should not be breastfed by mothers taking carbimazole.*"

Critique: Breastfeeding was proscribed in women taking either carbimazole (methimazole) or propylthiouracil until about 20 years ago.[20] On current data, treatment is safe in standard dosage, although carbimazole is detectable in breast milk.[16,21] Inadvertent over-treatment of lactating women produced no adverse effect on infants.[22] Propylthiouracil is often preferred to carbimazole as transfer to milk is less.[21]

Quality of evidence: Reference 16, 21, 22 (III-3, B).

Review of dosage

"*Once a remission has been secured, maintenance dosage should be continued for at least 12 months*, and up to two years of treatment may be required."

Critique: This recommendation is unclear and confusing, not based on any evidence and contrary to current practice. The response cannot be classified as *remission* while an antithyroid drug is still required. When *control* has been achieved, failure to decrease or cease dosage can result in serious iatrogenic hypothyroidism (see dose adjustment strategy for propylthiouracil).

Coordination with radioiodine

"Neo-Mercazole [Link] should be stopped temporarily *at the time of administration of radioiodine*."

Critique: This recommendation will limit the efficacy of radioiodine. Carbimazole needs to be stopped several days before and for several days after radioiodine administration,[8,9] to avoid blocking its incorporation into thyroglobulin (the same applies to propylthiouracil).

Quality of evidence: Reference 8, 9 (III-3, B).

PROPYLTHIOURACIL

Dose review and modification

"*After* control of thyrotoxicosis, the dose of propylthiouracil should be *gradually* decreased to 50 mg twice daily."

Critique: Dosage of both carbimazole and propylthiouracil needs to be reviewed and adjusted *before* achieving normal hormone levels. Delayed dose adjustment, as advised, can result in severe over-treatment. Dose reduction is appropriate when thyroid hormone levels decrease by 30%–50%.[8,9]

Quality of evidence: Reference 8, 9 (IV, C).

Breastfeeding

"*Breastfeeding should be terminated prior to initiation of therapy.*"

Critique: This recommendation was superseded by new data 20 years ago (see comment for carbimazole).[16,20,21] Propylthiouracil is often preferred to carbimazole because transfer to milk is less.[21]

Quality of evidence: Reference 16, 20, 21 (III-3, B).

Inaccurate explanation of mode of action

"Propylthiouracil blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) by inhibiting *incorporation* of iodide into tyrosine."

Critique: This conversion involves *removal* rather than incorporation of iodine.

Adverse effects incompletely documented

Further adverse effects of propylthiouracil are not listed:
1. Serious hepatotoxicity.[16,20]

2. Immune vasculitis syndrome, with positive antineutrophil cytoplasmic antibody.[16]

Quality of evidence: Reference 16, 20 (IV).

Maximum dosage

"Patients with severe hyperthyroidism *may require up to 2 g/day.*"

Critique: Dosage of 2 g daily has no record of safety. Dosage of 1200 mg daily is the upper limit recommended for severe hyperthyroidism or thyroid storm.[16]

Quality of evidence: Reference 16 (III-3, B).

LIOTHYRONINE

Unresponsiveness to thyroxine

"In myxoedema unresponsive to thyroid [extract] or thyroxine, liothyronine is essential."

Critique: There are no authenticated reports of acquired resistance to thyroxine, with retained responsiveness to liothyronine. Other causes of apparent unresponsiveness to thyroxine, such as poor compliance, impaired absorption and insufficient dosage of thyroxine, must be checked before considering liothyronine.

Other hypometabolic states

"In other conditions of the hypometabolic state, the usual daily dosage is 20 to 60 microgram divided and administered two or three times daily."

Critique: This appears to support use of liothyronine in *hypometabolic states other than hypothyroidism*. Such conditions have not been confirmed to exist, and this recommendation endorses a common mode of thyroid hormone misuse.[7]

MIMS = Monthly index of medical specialties annual.[3] *APPG = Australian prescription products guide.*[4] TSH = thyroid stimulating factor. "Quality of evidence" according to National Health and Medical Research Council (NHMRC) — level of evidence, I–IV; grade of recommendation, A–D.[12] ◆

Contentious points in PI-based sources for thyroid-related medications

There are numerous discrepancies when information on thyroid-related medications in the PI-based *June 2006 MIMS annual*, MIMS Online and *APPG 2006* is compared with the current medical literature and with Australasian[8,9] and international reviews.[10,11] Major points of contention that have a direct impact on patient care are summarised in the Box.

Where possible, evidence for the critiques of the PI has been presented according to the notation of National Health and Medical Research Council (NHMRC) guidelines (level of evidence [I–IV] and grade of recommendation [A–D]).[12] In some, the NHMRC level of supporting evidence does not appear high, as randomised trials have not been performed — many thyroid-related medications have been in use for decades and their introduction pre-dates stringent documentation. However, the currently available lower-level evidence has been confirmed in endocrinology clinical practice over many years and has been incorporated as current best practice.

Some examples of contentious points, which are discussed further in the Box, include:

- A healthy euthyroid adult need not experience a period of iatrogenic hypothyroidism after near-total thyroidectomy, as would occur if PI-based guidelines for commencement of thyroxine treatment ("*In all cases*, Oroxine [Sigma] should be initiated at not more than 50 microgram/day . . ." [eg, *MIMS annual* 2006. Oroxine. Precautions: Initiation of therapy]) were followed.
- Further, it is apparent from clinical practice that continuation of antithyroid drug without dose modification *until* a patient is shown to be euthyroid can lead to serious over-treatment. ("*After* control of thyrotoxicosis, the dose of propylthiouracil should be *gradually* decreased to 50 mg twice daily." [eg, *MIMS annual* 2006. Propylthiouracil. Use in pregnancy]). If a patient were then to abruptly stop the antithyroid drug either by own choice or on medical advice, the thyrotoxicosis would probably recur.
- The recommendation that liothyronine can be used for "myxoedema unresponsive to . . . thyroxine" and for "other conditions of the hypometabolic state" (eg, *MIMS annual* 2006. Tertroxin [Sigma]. Dosage and administration), is contentious and potentially harmful.[7] There is no evidence-based confirmation that this ill-defined group of conditions actually exists; this recommendation provides an apparent endorsement of a common mode of thyroid hormone misuse.[7]

Thus, if such recommendations for the use of thyroid-related medications, as espoused in the PI and thus in *MIMS* and *APPG*, were mistakenly interpreted as firm guidelines for prescribing practice, these texts would legitimise potential misuse of medication, while implying that several established therapeutic strategies are "off label".

Recommendations on the use of iodide

The formulation, source, dosage and adverse effects of iodide are not documented in *MIMS* or *APPG*; no PI has apparently been submitted, as there is no commercial sponsor. Nevertheless, these texts make imprecise or dubious recommendations for its use within the information pertaining to other thyroid medications.

The recommendation that high-dose iodide should be used routinely in preparation for surgery in thyrotoxicosis (eg, *MIMS annual* 2006. Neo-Mercazole [Link]. Dosage and administration — last paragraph) is erroneous. While short-term high-dose iodide does temporarily inhibit thyroid hormone release and reduces the vascularity of the gland in Graves disease, it has no beneficial effect on thyroid blood flow in toxic multinodular goitre (quality of evidence: III-2, B).[23] It should be noted that sustained iodide excess can exacerbate thyrotoxicosis and can impair the response to antithyroid drugs, with the potential for severe drug-resistant thyroid overactivity that may require emergency surgery (quality of evidence: IV, B).[24]

Of greater concern is the recommendation (eg, *MIMS annual* 2006. Neo-Mercazole. Use in pregnancy) that antithyroid drugs should be replaced by high-dose iodide in late pregnancy, a manoeuvre that is specifically contraindicated (quality of evidence: IV, B),[19] except in the occasional situation of preparation for surgery in the second trimester (quality of evidence: IV, B).[19] Iodide readily crosses the placenta and marked excess can severely impair fetal thyroid function, causing fetal goitre and neonatal hypothyroxinaemia, particularly in premature infants (quality of evidence: IV, B).[18,19] It should be noted that the iodide doses used for transient control of thyrotoxicosis, or to diminish thyroid vascularity in Graves disease, using Lugol's iodine, which contains 130 mg/mL of elemental iodine, are at least 100-fold greater than the 0.1–0.3 mg daily intake recommended for prevention of iodine deficiency in pregnancy (quality of evidence: III-1, A).[25]

Formulation of consumer medicine information

The TGA has initiated a consultancy to improve the range and quality of consumer medicine information (CMI), which it also endorses.[26] The preliminary discussion paper[26] defines PI as the benchmark for CMI. While that document acknowledges that problems arise if PI is not kept up to date,[26] there is no clear perception of any need to go beyond PI sources in preparing optimal CMI. That current PI-based sources can differ widely from contemporary therapeutic practice is a reality that should be considered in preparing CMI. Under present arrangements, CMI can be no better than the PI supplied by manufacturers or sponsors of repackaged imported products.

Mechanisms to improve and update PI and CMI

According to current regulations, initiatives to update or alter the PI of prescription medications require a manufacturer or sponsor to apply to the TGA and pay a fee for review of a revised submission.[27] The TGA does not normally initiate changes in PI. While there is some provision for a sponsor to make "self-assessable" changes in PI as defined,[27] it is unlikely that the problematic recommendations identified here could be altered by "self-assessable" revision under current regulations.[27] Thus, each of the four companies that market the medications listed in the Box would need to make a separate submission to the TGA to initiate revision; there is no commercial incentive to do so. The situation regarding iodide is unusual because it has no commercial sponsor; accountability for the suggestions on its use is undefined.

The quality of information on thyroid-related medications in the PI of each drug, and thus in *MIMS* and *APPG*, is deficient to an extent that requires prompt review. The established mechanisms for updating PI are unlikely to achieve this, especially as the accountability for some information in these texts is undefined. An initiative to revise out-of-date or inaccurate sections could involve Australian clinicians who observe the effects of thyroid-related

medications and are acquainted with relevant medical literature. Their advice can be sought, either directly through the Endocrine Society of Australia, or through the Therapeutics Committee of the Royal Australasian College of Physicians. A clearly defined, professional peer review process, the cornerstone of reputable medical literature, might improve the information currently available for both new and long established thyroid-related medications.

Addendum: Review of sequential *MIMS annuals* indicates that there has been no substantive change to the entries for carbimazole (Neo-Mercazole) or propylthiouracil since 1985. The entry for liothyronine (Tertroxin) was updated in 1988 and that for thyroxine (Oroxine) in 1990. Advice that dosage of thyroxine should be increased in pregnancy was added in 2004. Storage instructions for thyroxine were revised in 2006.

Competing interests

I received travel assistance from Abbott, manufacturer of thyroid products in the United States, to attend and present at the American Thyroid Association meeting in Vancouver (2004).

Author details

Jim R Stockigt, MD, FRACP, FRCPA, Endocrinologist,[1] Emeritus Consultant,[2] Professor of Medicine[3]

1 Epworth Hospital, Melbourne, VIC.

2 Department of Endocrinology and Diabetes, The Alfred Hospital, Melbourne, VIC.

3 Monash University, Melbourne, VIC.

Correspondence: jrs@netspace.net.au

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