An evaluation of the adequacy of outpatient monitoring of thyroid replacement therapy

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Abstract

Objectives Hypothyroid patients managed with excessive or insufficient thyroid replacement therapy are often difficult to clinically recognize. Monitoring may prevent or minimize the consequences of adverse drug events (ADEs). We sought to develop an explicit model of medication monitoring and to evaluate monitoring processes and ADEs in patients taking levothyroxine. Methods A retrospective chart review of 400 outpatients receiving levothyroxine therapy between 1 January 2000 and 1 January 2001 at a large North American tertiary care hospital. We measured the proportion of patients satisfying minimum monitoring criteria, experiencing specific monitoring errors and having levothyroxine-related ADEs. Explicit monitoring criteria were derived from the literature and through expert opinion. Adverse drug events were identified using structured implicit reviews. Results Overall, only 56% (95% confidence interval [95% CI] 51–62%) of the patients prescribed levothyroxine received the minimal recommended monitoring. Errors were identified at all stages of the monitoring model. Patients who received the recommended monitoring had fewer levothyroxine-related ADEs (1% vs. 6%, \( P = 0.013 \)) than those who did not. Minority status (white people 2% vs. black people 4% vs. Hispanics 14%, \( P = 0.023 \)) and primary language (English 3% vs. Non-English 20%, \( P = 0.002 \)) were the patient characteristics associated with levothyroxine-related ADEs. Conclusion Only half of outpatients taking levothyroxine at one tertiary care hospital received the recommended monitoring during one year of follow-up. Levothyroxine-related ADEs were more frequent in patients with lower-quality monitoring and in minorities and non-English speakers.

Introduction

Previous studies have shown that many patients on thyroid replacement therapy receive either excessive or insufficient supplementation (Ross et al. 1990; Canaris et al. 2000). These patients are at risk of various adverse drug events (ADEs), defined as injuries because of drugs (Singer et al. 1995; Braverman & Utiger 2000; Klein & Ojamaa 2001). Medication monitoring is one strategy that can be used to prevent or ameliorate the consequences of ADEs. However, previous studies suggest that tremendous variation exists in medication monitoring practices (Schiff et al. 1991; Schoenenberger et al. 1995; Kuper-
man et al. 1998; Canas & Tanasijevic 1999; Hougardy et al. 2000; Abookire et al. 2001). Some patients receive excessive monitoring that can result in inappropriate investigations, with consequences of substantial costs or even risk to personal health (Schoenenberger et al. 1995; Canas & Tanasijevic 1999). Other patients receive inadequate monitoring and may be at greater risk of ADEs (Hougardy et al. 2000). However, even among those patients with appropriate medication surveillance, providers often fail to respond to important symptoms, signs and laboratory abnormalities (Schiff et al. 1991; Kuperman et al. 1998; Abookire et al. 2001). The Medical Practice Study identified medication-monitoring errors as a common cause of preventable ADEs, suggesting that appropriate medication monitoring may reduce ADE rates (Leape et al. 1991).

Therefore, we undertook a study to examine the epidemiology of outpatient levothyroxine monitoring with the following goals:

1. to develop a simple and explicit model of medication monitoring that would facilitate reliable data collection;
2. to use this model to determine at what medication monitoring stages most errors occur, and
3. to assess the incidence and preventability of ADEs associated with monitoring errors.

Methods

Monitoring model

To facilitate this study we developed a simple model of medication monitoring consisting of four stages: initiation of therapy, surveillance, surveillance response and follow-up visits. Initiation of therapy (Stage 1) begins with a prescription, patient education and baseline evaluations. This is followed by surveillance (Stage 2) with clinical observation and laboratory investigations. Surveillance results then must be communicated to providers, reviewed, and responded to appropriately (Stage 3). Periodic patient–provider follow-up visits in person are often required (Stage 4).

Development of monitoring criteria

English-language studies involving the monitoring of levothyroxine therapy were identified by reviewing the following Medical Subject Heading keywords in MEDLINE from 1966 through 2000: drug monitoring, levothyroxine, appropriateness criteria, clinical laboratory and consensus conference. Articles providing explicit monitoring standards for the management of primary hypothyroidism in adult outpatients were selected (Singer et al. 1995; AACE Thyroid Task Force 1995; Vanderpump et al. 1996). The monitoring criteria [Table 1] were derived based on the information obtained from the literature search and were then revised by two internists (H.T.S. and D.W.B.) and one endocrinologist (A.S.). The aim was not to produce inclusive clinical guidelines, but to establish simple operational monitoring criteria that could be used as boundary rules (McDonald & Overhage 1994).

Patient sampling and data collection

All outpatients with a medical record diagnosis of primary hypothyroidism, an active prescription for levothyroxine and a primary care doctor at Brigham...
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and Women’s Hospital on 1 January 2000 (point prevalence) were eligible for inclusion. Patients with thyroid cancer, nodular thyroid disease, subacute thyroiditis, secondary hypothyroidism or subclinical hypothyroidism were excluded. Patients with a primary care doctor at another institution were also excluded. Four hundred patients were then randomly sampled from the population satisfying the study criteria. These patients then had their outpatient medical records abstracted for the period beginning 1 January 2000 and ending 1 January 2001.

Medical records were reviewed by one author (J.F.) to obtain baseline patient information as of 1 January 2000. Levothyroxine monitoring processes were abstracted from the medical record and compared to our explicit pre-specified criteria. Each patient was classified as satisfying or failing to satisfy the monitoring criteria. A single doctor (H.T.S.) reviewed all patients’ medical records for ADEs using a structured implicit review instrument derived from the ADE Prevention Study (Bates et al. 1995). The reliability of the monitoring and ADE judgements was separately evaluated by a second blinded doctor (S.B.A.) who independently reviewed two mutually exclusive 10% random samples of medical records.

Data analysis

Descriptive statistics were used to examine the results of the monitoring model. To determine which clinical characteristics were associated with adherence to monitoring recommendations and ADEs we used chi-square tests, Fisher’s exact test and multivariable logistic regression models. In evaluating ADEs, only univariate analyses were performed because of the limited number of events. Statistical significance was defined as a 2-tailed P-value < 0.05 for all analyses. Agreement on medical record abstraction was assessed with Cohen’s kappa reliability coefficients (Landis & Koch 1977). The Splus statistical package (Splus 2000 Professional Release 2. Math Soft Inc.) was used for all statistical analyses.

Results

We identified 3208 outpatients at Brigham and Women’s Hospital who were receiving levothyroxine on 1 January 2000, among whom 1385 satisfied our study criteria. Following a detailed review of the 400 randomly selected patients, it was found that 7 patients were no longer taking levothyroxine, 3 patients had thyroid cancer, 3 patients had secondary hypothyroidism and 24 patients had primary care doctors at other health care organizations, leaving 363 patients. Data were missing on patient ethnic background for 108 patients, on levothyroxine dose for 2 patients and primary language for 1 patient. Complete data were available for all remaining patients. The kappa reliability coefficients for the interrater agreements for monitoring processes and ADEs were 0.89 and 0.75, respectively.

Baseline characteristics

The mean age of the patients was 54 years (range 20–94 years), 92% were women, 58% white people and most spoke English (96%). Levothyroxine was prescribed at a mean daily dose of 106 micrograms (range 25–250 μg) for management of autoimmune thyroid disease (86%), postablative hypothyroidism (10%), postexternal beam radiation induced hypothyroidism (2%) and medication induced hypothyroidism (2%). The median duration of levothyroxine therapy prior to the study onset was 59 months (range 1–756 months). Patients received on average 6.4 prescription medications (range 1–21) and had a mean Charlson Index score of 1.0 (range 0–8) (Charlson et al. 1987).

Levothyroxine monitoring

The 363 patients had a total of 1400 monitoring criteria during the one-year study period of which 1183 were satisfied (15.5 monitoring errors per 100 criteria, Table 2). Errors were identified at all stages of the monitoring model. Two hundred and sixty-four patients had levothyroxine therapy initiated prior to establishing care at Brigham and Women’s Hospital, leaving 99 patients whose baseline evaluations could be examined and used in calculating cumulative monitoring success. Among these patients only 53 (53% [95% CI 43–63%]) satisfied all of the monitoring criteria [Fig. 1].

Patients who adhered to the monitoring recommendations had fewer monitoring criteria on average than those who did not (3.2 vs. 4.2, P < 0.001); this difference was largely explained by a greater mean...
number of abnormal thyroid-stimulating hormone (TSH) results (0.2 vs. 0.8, \(P = 0.007\)). Patients who adhered to the monitoring criteria also had a lower mean dose of levothyroxine prescribed than patients with monitoring errors (102 mg per day vs. 111 mg per day, \(P = 0.023\)).

Adverse drug events

Twenty-four patients (7%) experienced an ADE during the study period. Twelve of the patients (3%) developed an ADE related to levothyroxine. Among the patients with levothyroxine-related ADEs: 6 events were secondary to excessive supplementation while 6 were secondary to insufficient supplementation. Five (42%) patients experienced temporary disability from their levothyroxine-related ADEs: depression \((n = 3)\), unstable angina \((n = 1)\) and atrial fibrillation \((n = 1)\). Seven patients (58%) had only symptoms: palpitations \((n = 2)\), weight loss \((n = 1)\), headaches \((n = 1)\), fatigue \((n = 1)\), cold intolerance \((n = 1)\) and delayed elective surgery \((n = 1)\). No injuries resulting in permanent disability or death were documented. Nine of the 12 ADEs (75%) were classified as preventable.

Minority status was associated with a higher risk of a levothyroxine-related ADE [white people 2% (4/210) vs. black people 4% (1/27) vs. Hispanics 14% (2/14), \(P = 0.023\)]. Patients whose primary language was not English were also at increased risk of a levothyroxine-related ADE [20% (3/15) vs. 3% (9/348), \(P = 0.002\)]. Patients whose management adhered to the monitoring criteria had fewer levothyroxine-related ADEs [1.0% (2/205) vs. 6.3% (10/158), \(P = 0.013\)] than those who did not. This difference was largely accounted for by preventable ADEs [0% (0/205) vs. 5.7% (9/158), \(P = 0.002\)]. No differences were observed for non-preventable levothyroxine-related ADEs [1.0% (2/205) vs. 0.6% (1/158), \(P > 0.2\)] or ADEs associated with other medications [3.9% (8/205) vs. 3.2% (5/158), \(P > 0.2\)].

Discussion

In this study, we developed an evidence-based model for evaluating outpatient medication monitoring. When the model was applied to patients receiving levothyroxine we found that only half of the patients satisfied all the criteria. Most monitoring errors occurred during the surveillance and surveillance response stages. Levothyroxine-related ADEs were more frequent in patients with lower-quality monitoring and in minorities and non-English speakers.
The results of this study should be interpreted within the context of its limitations. First, our data were obtained through retrospective medical record review, limiting collection to measures recorded in the chart. This limited our ability to accurately identify monitoring processes and ADEs. Second, our monitoring criteria have not been validated. While the criteria were developed through a synthesis of literature review and expert opinion they were designed to be simple operational boundary rules rather than clinical practice guidelines. Finally, data collection involved the outpatient clinics affiliated with a single teaching hospital and may have limited generalizability to other settings.

Only half of outpatients taking levothyroxine at one tertiary care hospital received the recommended monitoring during a one-year study period. Our study model identified errors at all monitoring stages. These data highlight the challenges of outpatient prescription medication monitoring. Carefully
coordinating patients, providers and laboratory investigations is not easy, particularly in the outpatient setting with its limited redundancy and many degrees of freedom. However, while medication monitoring may intuitively make sense and be recommended for drugs such as levothyroxine, there is little evidence that monitoring actually improves outcomes. Understanding the nature of monitoring errors and the associated ADEs is a first step towards improving medication monitoring and drug safety.

Acknowledgements

Dr Stelfox was supported by a Postdoctoral Fellowship award from the Canadian Institutes of Health Research, a Walker Fellowship from Harvard Medical School and the Clinician-Scientist Program of the Department of Medicine at the University of Toronto. Dr Bates has been supported in part by an RO1 (HS11169) and PO1 (HS11534) grant from the Agency for Healthcare Quality and Research, Rockville, MD. We thank Dr Anna Sawka for helping us revise the levothyroxine monitoring criteria and for reviewing an earlier version of the manuscript.

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