Ionic versus nonionic contrast media: A burden or a bargain?

Amiram Gafni, PhD; Carl J. Zylak, MD

Clinicians, economists, health care providers and policy decision-makers have recently become very interested in a new generation of contrast agents used in diagnostic radiology because of increased costs and doubts about the value of gains. Goel, Deber and Detsky[1] have argued that an economic analysis comparing the old (ionic) with the new (nonionic) agents brings into question the policy in Ontario of providing nonionic contrast media universally. According to their findings a complete conversion to the new media would result in an incremental cost of at least $65 000 to gain 1 quality-adjusted life-year (QALY). This is a high cost-utility ratio that "might save some identifiable victims at the expense of a larger number of unidentifiable ones".[1]

The paper of Goel and associates is unique because it considered both the survival and the quality-of-life effects of contrast media and tried to account for them in the analysis through the use of QALYs as the unit measure of outcome. Our aims are (a) to alert the reader to potential problems associated with QALYs, (b) to describe a different outcome measure, healthy years equivalent (HYE),[2] (c) to show how the use of QALYs has predetermined the outcome in Goel and associates' study, (d) to identify quality-of-life effects that were assumed to be negligible and (e) to illustrate how the use of HYE might alter the results of Goel and associates.

QALYs versus HYE

Decisions on medical treatments and health programs involve technical and value judgements. One important evaluation concerns the trade-off between quality and length of life, another compares positive treatment effects (benefits) with negative ones (risks). The most commonly used measure of outcome in the economic evaluation of health care programs is the number of QALYs gained, which has the advantage of providing a common unit of measure for comparison across programs. Furthermore, this unit of outcome enables us to compare programs that affect both quality of life and length of life, since it combines both of these factors.

In brief, QALY is a health status index that uses a weighting scheme. Each definable health state is assigned a weight from 0 (death) to 1 (full health). The time spent at a given health state is multiplied by the corresponding weight and added to similar values for other health states, to yield a number of QALYs. One approach that incorporates patient preferences in the process of decision-making and that measures the weights to be used in the QALY calculation is the utility approach, considered by many to be the most credible method.[3]

Ignoring patient preferences in decision-making can result in the wrong choice of service.[4-6] Thus, the use of QALYs is very appealing, since it reflects the relative desirability of different health states to those whom we believe are supposed to benefit from health care services. A detailed description of the different methods to measure QALYs can be found elsewhere.[7]

A recent paper showed that different methods chosen to create the QALY index resulted in an outcome measure that was not necessarily consistent with patients' preferences.[2] This misrepresentation could lead to the choice of the nonpreferred alternative; for example, alternative A may be the calculated preference even though the patient's stated preference is alternative B.[2,8] Another measure, the HYE,[2] more fully reflects individual patients' preferences and so avoids such discrepancies. Like QALYs it

From the Centre for Health Economics and Policy Analysis, Department of Clinical Epidemiology and Biostatistics, and the Department of Radiology, Faculty of Health Sciences, McMaster University, Hamilton, Ont.

Reprint requests to: Dr. Amiram Gafni, Department of Clinical Epidemiology and Biostatistics, Rm. 2C12A, McMaster University Health Sciences Centre, 1200 Main St. W, Hamilton, Ont. L8N 3Z5

combines the outcomes of both quality and quantity of life and thus serves as a common unit of measure for all programs.

Another recent review[9] highlighted the critical issues concerning the use of QALYs to measure the outcome of health care decisions related to both individual patient care and social resource allocation. The authors concluded that the QALY measure failed to account for some of the critical factors that affect preferences for different health care choices. They did not, however, suggest an alternative.

Let us explain why the QALY measure does not necessarily adequately measure patient preferences for quality-of-life outcomes resulting from different contrast media. In calculating QALYs the utility value of the health state, expressed as a weight, is multiplied by the duration in that health state. This method implicitly assumes that very painful but very short events do not matter to the patient (i.e., they are of negligible effect). The following example illustrates this claim.

A person has 30 years to live but has to go through a very painful test that takes 1 hour on average. When asked, the person rates his or her quality of life during the test as being close to death (0.05 when death is defined as 0). Calculating the QALY value of living 30 years in full health, interrupted by a very painful examination, we find that it is equal to 0.05(0.000114 yr) + 1.0(30 yr − 0.000114 yr) = 29.9999. (Note that 1 hour is equal to 0.000114 year and that discounting was ignored, as was done by Goel and associates.)

It is easy to see that the effect of suffering 1 hour of severe pain is negligible.

The assumption that patient preferences are such that the conversion of time in "ill health" to time in "full health" is linearly related to the time spent in the state of ill health is very restrictive. It leads, as in the example, to the arbitrary reduction of a bad state to a negligible effect on the person's overall quality of life and is not supported by empiric evidence.[9] Unlike QALY the HYE does not make such a restrictive assumption and hence allows people to reveal their true preferences. The HYE can be measured, for example, through the use of a two-stage procedure[10] that uses the standard gamble (SG) method, a lottery-based technique to reveal preferences under uncertainty. The SG method is considered the classic method, or the "gold standard", for measuring cardinal preferences.[3]

For the example of the very painful test, in the first stage the person is offered two alternatives. The first is a lottery with two possible outcomes: full health for 30 years (probability p) or immediate death (probability 1 − p). The second alternative offers a certain outcome of having a very painful 1-hour test followed by life in full health for the remaining 30 years. Probability p is varied until the person is indifferent to either alternative. At this point the person's preference value of living 30 years (minus 1 hour) in full health interrupted at the beginning by a very painful 1-hour examination is equal to p* (the value of the probability at the indifference point).

In the second stage lottery questions are used again to convert the time in ill health, which includes the painful examination, to time in full health (HYEs). The person is offered two alternatives. The first is a lottery with two possible outcomes: full health for 30 years (probability p*) or immediate death (probability 1 − p*). The second alternative is the certain outcome of living H more years in full health, H being varied until the person is indifferent to either alternative. H* denotes the value of H at the indifference point and represents the hypothetical number of years in full health, which is the equivalent of the person living 30 years (minus 1 hour) in full health, interrupted at the beginning by a very painful 1-hour examination.

This two-stage procedure to measure HYE does not assume any specific preference pattern, as is the case for calculating the QALY index. It allows the person to reveal his or her true preferences through answers to the lottery questions; this will prevent the kinds of discrepancies that can arise from QALY calculations.[2,8]

If the procedure we have described (or other procedures) to measure HYE is used, the person in our example might reveal a preference for trading a month (0.0834 year) of life to avoid the pain of the test; this would result in 29.9166 years of full health instead. This interpretation assumes, as did Goel and associates, a zero time preference (i.e., no discounting). Some people will argue that giving up 1 month of life out of 30 years is a high price to pay, whereas others will argue that for the case in question it is a low price to pay; this empiric question has to be tested with an outcome measure that allows people to reveal their true preferences. It is an important task, because, as demonstrated in the next section, a much smaller price paid by people to avoid pain and discomfort can change the results of the economic analysis by Goel and associates.

Recalculating the cost-utility ratio

Goel and associates structured the problem as a decision tree with two outcomes: costs and clinical effects. Three choices (strategies) were available at the decision node: (a) to continue to use the old contrast media in all patients, (b) to administer the new media to all patients and (c) to administer the new media only to high-risk patients. In our analysis we chose only two options, since they represent the past (all patients received the old contrast media) and the present (all patients receive the new contrast media) in Ontario. In each case the possible clinical effects identified by Goel and associates were as follows: "The patient could either survive with no reaction or suffer a minor reaction (not leading to prolonged hospital stay or permanent disability), a major reaction (leading to prolonged hospital stay and disability) or a fatal reaction." Baseline probabilities obtained by them from the literature were 1 in 20 procedures for minor reactions, 1 in 10 000 for major reactions and 1 in 40 000 for death. Goel and associates assumed a 10-fold reduction in the relative risks for all types of reaction to the new media.

For the baseline case Goel and associates used an average life expectancy of 30 years after the administration of contrast media. Using a utility scale of 0 for death and 1 for perfect health they arbitrarily assigned a value of 0.7 to all the remaining life-years for patients suffering major reactions. They did not mention the preference value attributed to the outcome of minor reaction and no reaction. However, they clearly assumed negligible effect. Goel and associates found that the mean QALY for the ionic contrast media arm was 29.9986 years and for the nonionic 29.9999 years, for a net gain of 0.0013 QALY. The costs associated with each arm were $14.3872 for the ionic contrast media and $97.5388 for the nonionic media, for a net cost of $83.1516. The marginal cost–utility ratio (the net cost divided by the net gain) was $63 963 per QALY gained.

The reason for such a big ratio is mainly that, under their assumptions, Goel and associates arrived at a very small net gain (0.0013 QALY) from using the nonionic contrast media rather than the ionic ones. Thus, the division of the net cost ($83.15) by such a small gain resulted in a huge marginal cost–utility ratio. Against this background we now show that the choice of QALYs as the outcome measure has predetermined the results of the analysis. In other words, the results of their economic evaluation are very sensitive to the assumptions about the values that people assign to the different outcomes on the different arms of the decision tree.

To demonstrate this effect we re-evaluated the outcomes using the same decision tree, the same set of probabilities and the same set of costs as Goel and associates used. The only difference is that QALY was replaced with HYE as the measure of outcome. As in the study by Goel and associates values were arbitrarily assigned to the possible outcomes and used to recalculate the marginal cost–utility ratio for ionic and nonionic contrast media administered to all patients.

We assigned a value of 0 HYE for the outcome of death and 21 HYE for the outcome of major reaction. These are the same values as the QALYs assigned by Goel and associates. We used the same value because the probability of a major reaction occurring is so low (1/10 000 in the ionic arm and 1/100 000 in the nonionic arm) that in practice major changes in the assigned value are unlikely to affect the result of the analysis.

The definitions of minor and major reactions used by Goel and associates differed from the most commonly used ones.[11-14] In most clinical studies a four-category classification is used that includes death, severe reactions (shock, anaphylactic effects, pulmonary edema, cardiac arrest and myocardial infarction), intermediate reactions (severe vomiting, dyspnea, chest pain and seizures) and minor reactions (faintness, heat, pain, nausea and limited urticaria). It is not easy to match the two classification systems. The minor reaction group in Goel and associates' study included both the intermediate and the minor reaction groups of the four-category classification system. We assigned a value of 29.98 HYE to the minor reaction group of Goel and associates. This value can be interpreted as patients' willingness to trade 0.02 years of life (from their remaining 30 years) to avoid the consequences of minor reactions.

The no reaction group was the most difficult one to which we had to assign a value. Supposedly, patients in this group are unable to tell whether they received the ionic or the nonionic contrast media. This has not yet been studied to the best of our knowledge. The side effects recorded describe at best what clinicians (radiologists in most cases) think should be recorded. However, when pressed many of them admit that most patients hardly feel anything when injected with the nonionic contrast media, whereas most feel uncomfortable when injected with the ionic contrast media. Although only anecdotal this evidence should be easy to check in a scientific study. Assuming that these reports are true, to the outcome of no reaction we assigned a value of 29.998 HYE for the ionic contrast media and 29.999 for the nonionic ones. The reason that 30 HYE was not assigned in each case is that having to go through any examination reduces a person's quality of life. The difference in outcome between the two types of contrast media represents the assumption that patients who have 30 more years to live would be willing to give up a few hours of their lives to have the nonionic contrast media instead of the ionic.

We multiplied these HYE values by the set of probabilities provided by Goel and associates to find the mean HYE value for each arm. The mean value for the ionic contrast media arm was 29.99545 and for the nonionic arm 29.99874. The net gain (marginal HYE) from using the nonionic contrast media rather than the ionic ones was 0.00329 HYE, as compared with 0.0013 QALY. Dividing the net cost of $83.15 determined by Goel and associates by the marginal HYE we found that the marginal cost-utility ratio was $25 274 gained, as compared with $63 963 per QALY gained.

The cost-utility ratio found by Goel and associates of about $22 000 per QALY gained for providing nonionic contrast media only to high-risk patients was considered by the authors to be reasonable from a societal perspective. Because both QALYs and the HYE are measures used to convert years in ill health to years in full health one can interpret this claim as follows: the price of $22 000 for 1 year of life in full health is a reasonable one to pay from a societal perspective. Therefore, the cost-utility ratio of $25 274 per HYE gained for providing nonionic contrast media to all patients might be considered reasonable as well.

Discussion

Goel and associates claimed that the policy in Ontario of providing nonionic contrast media universally was questionable on the basis of their economic evaluation. This claim was not supported by sound methodology and evidence. Patient preferences for all potential outcomes were not measured but were arbitrarily assumed, and in some cases they were assumed to have a negligible effect. More important, because of strong assumptions about preferences QALY is insensitive to the side effects of short-term treatment. The choice of this measure has, in our opinion, predetermined the result of the analysis.

Using the HYE, a more sensitive outcome measure that better reflects patient preferences, and attributing values to all potential outcomes (even in an arbitrary way, as done by Goel and associates) we have shown that an economic evaluation might result in a much lower cost-utility ratio. This ratio might even be acceptable to Goel and associates. This is an important finding since society's willingness to fund the universal use of nonionic contrast media depends, among other things, on its price in terms of resources used per year of life in full health gained. Thus, the relative cost-utility ratio (the price) is important to the decision-making process. A study that involves actual measurement of individual preferences and uses more powerful and sensitive measures of outcome should be performed before conclusions are drawn.

In general, factors other than economic ones also affect policy development. These factors were discussed by Goel and associates with regard to the decision to provide nonionic contrast media for all patients in Ontario. We believe that the economic aspect is not the dominant one in the process of policy decision-making. The results of a well-designed and well-executed economic evaluation are one input to the process of policy decision-making. Because they are important, the analysis must be done properly.

References

1. Goel V, Deber RB, Detsky AS: Nonionic contrast media: economic analysis and health policy development. *Can Med Assoc J* 1989; 140: 389-395
2. Mehrez A, Gafni A: Quality-adjusted life-years, utility theory and healthy-years equivalents. *Med Decis Making* 1989; 9: 142-149
3. Torrance GW: Measurement of health state utilities for economic appraisal. *J Health Econ* 1986; 5: 1-30
4. McNeil BJ, Weichselbaum R, Pauker SG: Fallacy of five-year survival in lung cancer. *N Engl J Med* 1978; 299: 1397-1401
5. Ben Zion U, Gafni A: Evaluation of public investment in health care: Is the risk irrelevant? *J Health Econ* 1983; 2: 161-165
6. Mehrez A, Gafni A: The optimal treatment strategy: a patient's perspective. *Manage Sci* 1987; 33: 1602-1612
7. Drummond MF, Stoddart GL, Torrance GW: *Methods for the Economic Evaluation of Health Care Programmes*, Oxford Med Publ, Oxford, 1987
8. Gafni A: The quality of QALYs (quality-adjusted life-years): Do QALYs measure what they at least intend to measure? *Health Policy* 1989; 13: 81-83
9. Loomes G, McKenzie L: The use of QALYs in health care decision making. *Soc Sci Med* 1989; 28: 299-308
10. Mehrez A, Gafni A: *Healthy Years Equivalent: How to Measure Them Using the Standard Gamble Approach* (working paper 22), Centre for Health Economics and Policy Analysis, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ont, 1989
11. Shehadi WH, Toniolo G: Adverse reactions to contrast media. *Radiology* 1980; 137: 299-302
12. Schrott KM, Behrends B, Clauss W et al: Iohexol in der Ausscheidungsurographie. *Fortschr Med* 1986; 104 (7): 153-156
13. Goldberg M: Systemic reactions to intravascular contrast media: a guide for the anesthesiologist. *Anesthesiology* 1984; 60: 46-56
14. Katayama H, Kozuka T, Takashima T et al: Adverse reactions to contrast media: high-osmolality versus low-osmolality media [abstr]. *Radiology* 1988; 169 (P) (suppl): 421