Pharmacoepidemiological modelling: Markov models of antibiotic use in patients with diabetes

H.G.M. Leufkens

The importance of time patterns in drug exposure is increasingly recognised in the evaluation of determinants and outcomes of pharmacotherapy. Data on patterns of drug exposure over time in individual patients and populations have been found to provide important 'fingerprint' information on temporal relations between disease course and severity, drug effects, and prognosis. However, data on prescriptions of medicines always need to be interpreted in the light of complementary data on clinical status, diagnosis, co-morbidity and the like.

TIME PATTERNS IN DRUG EXPOSURE

Research on patterns of drug exposure in pharmacoepidemiology shows three phases. In the first phase, drug exposure was a simple dichotomous 'yes/no' (or 'on/off'). In the second phase, the inclusion of dosing information made it possible to interpret findings in relation to dose-response characteristics. Nowadays, the focus has shifted to patient profiles and drug-usage patterns over time as important determinants of treatment outcomes. To exploit this principle in pharmacoepidemiology, reliable information on the time-sequence of initial and refill dispensing of drugs, switching patterns between and within individual drugs and drug classes, and discontinuation of drug therapy episodes is required. Interest focuses not only on the legend duration of exposure, but also on periods prior to and after such so-called 'time-windows'.

MARKOV MODELLING OF DRUG EXPOSURE PATTERNS

Walker and Chan applied Markov models to evaluate time patterns of exposure to nonsteroidal anti-inflammatory drugs (NSAIDs), providing a useful concept for learning about the dynamics of drug usage and the outcomes of therapy. NSAIDs as a drug class show significant variability in usage patterns, with important inter-drug variation regarding time-dosing, duration of use, switching behaviour, and the like.

Markov models are very suitable for analysing transitions from one drug use to another. A stationary Markov chain of the first order with a finite number of states corresponding to the number of antibiotic drugs was used as a model. A first step in Markov modelling to evaluate drug-use patterns is the definition of all distinct states of drug use: non-use, use of drug A, use of drug B, use of drug C, etc. A Markov chain represents a system of elements making a transition from one state to another over time. The first-order Markov chain means that the next future dispensing of the Markov chain depends only on the present and not on the passed dispensings. Conditional probability of state j, given state i, is called transition probability from state i to state j. (The transition probability is a conditional probability for the system to go to a particular new state, given the current state of the system). Stationary Markov chains may be applied only if the transition probabilities can be assumed as constant. This requirement is realistic only for states with a short time horizon, as is the case with most on-demand use of NSAID and regular treatment courses with antibiotics.

Markov modelling can be used to investigate the transitions among individual drugs and the status of 'non-use'. Transitions are classified as 'initiations', 'repeats', 'switches' and 'terminations', usually within a time-window of six months' follow-up (*table 1*). Moreover, in the follow-up of the work of Walker and Chan equilibrium values can be calculated on the basis of the full array of dispensings in the form of the table. The equilibrium state is reached

Table 1
Matrix of drug dispensings

		DRUGS SWITCHED TO				TOTAL
		No use	Drug A	Drug B	. .	R_o
	No use	a_{oo}	a_{o1}	.	.	R_o
DRUGS FROM	Drug A	a_{1o}	a_{11}	.	.	
	Drug B	.	.	. a_{ij}	.	R_j
	.	.	.	. .	.	.
TOTAL	C_o	C_o	C_1	C_j		N

a_{ij} = initiation if i=o and j≠o, a_{ij} = repeat if i=j, a_{ij} = switches if i≠o and i≠j, a_{ij} = termination if i≠o, and j=o.

when the distribution of drug dispensings remains the same after a cycle of next transitions ('stationarity'). Next, transition probabilities for stationary Markov chains can be estimated, providing 'predictive' information on the future state of drug use.

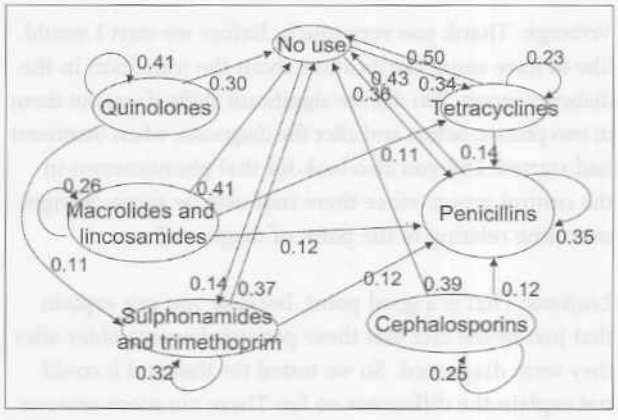
The transition probabilities can be arranged in the form of a transition matrix. The matrix is quadratic: its elements are non-negative and the row sums are 1.

CASE: USE OF ANTIBIOTICS IN DIABETIC PATIENTS

There is ample belief that diabetic patients are more prone to infections. However, the association between diabetes mellitus and increased susceptibility to infections in general is not supported by strong evidence. Still, Joshi et al. conclude that many specific infections are more common in diabetic patients, and some occur almost exclusively in them. Moreover, they state that many infections in diabetic patients occur with increased severity and are associated with an increased risk of complications.

Pharmacoepidemiological data on the use of antibiotics in diabetic patients is not consistent. Isacson et al. found in Sweden over the year 1977 a proportion of antibiotic users in type-1 diabetics aged 55-64 years of 17%. In type 2 this proportion was 23%, while only in 12% of non-diabetics were antibiotic prescriptions seen in the same year. Scottish data from 1955 also show an increased risk of needing antibiotic prescriptions in diabetics when compared to non-diabetics (type 1 relative risk of 1.76 (95% CI 1.67-1.85) and type 2 relative risk of 1.70 (95% CI 1.68-1.72)). However, Rathman et al. reported that in German clinical practice (1994) the prevalence of treatment with antibiotics in diabetic patients was 23.7% versus 26.8% in non-diabetic patients.

Markov modelling of the transitions of antibiotic use in diabetics in different phases of disease course is explored to make possible further elucidation of the association between diabetes and infection risk. In total, antibiotics are classified into six categories: tetracyclines (ATC code=J01A), penicillins (ATC code=J01C), cephalosporins (ATC code=J01D), sulphonamides and trimethoprim (ATC code=J01E), macrolides and lincosamides (ATC code=J01F), and the quinolones (ATC code=J01M). By including a 'non-use' state, the transition matrix consists of seven rows and columns, i.e. 49 cells. *Figure 1* depicts the transition probabilities on the basis of about 20,000 dispensings for antibiotics in a subset of patients with diabetes type 2. This map provides value information on the 'routing' of antibiotic use in this population of patients.



Figuur 1
Transition probabilities of antibiotic use in diabetics

For example, repeats of quinolones occur fairly frequently in diabetics (probability of 0.41), while penicillins are rarely prescribed in the six months after the patient has started treatment with sulphonamides or trimethoprim (probability of 0.12).

COMMENT

Modelling of transitions from one state to another provides a sensitive way of evaluating drug-use patterns over time.

Transition models require complete and reliable data on all individual drug dispensing. The Dutch pharmacy system provides an important resource for such studies as virtually all patients frequently visit a single pharmacy, as is for certain the case with patients with chronic diseases including diabetes mellitus.

With respect to the Markov model, we assume stationarity over time. This means that the transition probabilities should not vary over time. This will not always be feasible, as the pharmaceutical market-place is rather erratic by nature. However, classification of the transition states in the six categories of antibiotics will provide stability to the analysis, as most time-dependent variability is on an individual drug level and by class.

The challenge of this approach lies in the clinical interpretation of the models. For sure, transitions among drugs never occur in a random fashion. The interpretation of Markov models to produce relevant data and conclusions for the medical practitioner remains an important target for future research.

REFERENCES

- Chan KW, Walker AM, Yood RA. An equilibrium model of drug utilization. J Clin epidemiol 1993;46:113-21.
- Leufkens HG, Urquhart J. Variability in patterns of drug usage. J Pharm Pharmacol 1994;46:433-7.
- Lindsey JK. Models of Repeated Measurements. Oxford University Press, 1999.
- Staa TP van, Abenheim L, Leufkens HG. A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. J Clin Epidemiol 1994;47:183-9.
- Taylor HM, Karlin S. An introduction to Stochastic Modeling. Academic Press Inc., 1984.
- Vandenbroucke JP. Should we abandon statistical modeling altogether? Am J Epidemiol 1987;126:10-3.
- Walker AM, Chan KW, Yood RA. Patterns of interchange in the dispensing of nonsteroidal anti-inflammatory drugs. J Clin Epidemiol 1992;45:187-95.

Discussion following lecture of H.G.M. Leufkens

Verbrugh: Thank you very much. Before we start I would like to have some clarification about the transition in the diabetics group. You did see significant shifts if you cut them in two phases, before and after the diagnosis, when treatment had started. Did you also look for that phenomenon in the control group, since there may also be some changes over time relating to the point of diagnosis?

Leufkens: That is a good point, because you can explain that just by the fact that these patients became older after they were diagnosed. So we tested for that and it could not explain the difference so far. There are more reasons why we know that the moment patients are diagnosed for diabetes type 2, there is a general increase in prescriptions. We know from various studies, including studies of our own, that prescriptions induce more prescriptions. The moment the patient is in the ward and there is a reason to prescribe for instance diabetic therapy and also for cardiovascular diseases, the likelihood that you will also prescribe an antibiotic therapy becomes much higher.

De Marie: Perhaps it could have something to do with the eliciting of the clinical manifestation of diabetes through an infection: in particular, a urinary-tract infection can make diabetes manifest to the clinician, and that is why you see that shift to a higher prescription rate. That may be an explanation.

Leufkens: That is very interesting. We could look at the sequence: what came first, diabetes diagnosis or infection diagnosis? I think that is a very useful suggestion to look at, because the data are there.

Nagelkerke: Why did you have zero/zero transition in that matrix from the non-drug users? Is that because you did not include anyone who did not use any antibiotics?

Leufkens: The point is, when you look at the transition and you follow the patient during those next six months and you see no prescription of an antibiotic, then this patient goes from an antibiotic to non-use. The same is true, and vice-versa, when there is a start, but the patient is coming from non-use instead of coming from another prescription, so then there is a transition from non-use to an antibiotic.

Nagelkerke: That means that patients who never used antibiotics are not included?

Leufkens: That is correct.

Nagelkerke: That also means that there is no state of equilibrium, because you do a lot of conditional matrix and by multiplying them you do not get any equilibrium at all.

Leufkens: I completely agree with you, as I said before, that we have to solve that, because from various points of view the non-use group is very relevant. For instance, most of the tetracycline users come from non-use, but most of the quinolone transitions come from other antibiotics.

J. Vandenbroucke: I would go with a previous remark of the Chairman, and I would like to probe this a little bit further. As far as I know, the usual set-up of these studies is that the non-diabetic controls are age-matched and period-matched, meaning that they come into the database at the same time as the diabetes patients and are of the same age at the same time.

Leufkens: They were also matched by practice.

J. Vandenbroucke: If you took the date the diabetes was diagnosed in the index persons and artificially allotted it to the control persons (or even an average date), then you could do the exercise of going back.

Leufkens: Absolutely, I take that point. I think that is a very useful one and a possible explanation why we see that difference.

J. Vandenbroucke: In your database you have very often used the use of drugs as a proxy for disease. Nevertheless, I wonder whether the in-patient use of antibiotics and hospital diagnosis would not give a better approximation of bacterial infections in diabetic persons than the out-patient use of antibiotics. I am wondering about this, but I would like to ask the clinicians.

Leufkens: Most of the patients were 65 and older. When you look at the hospitalisations, most of them have a cardiovascular background and are not so much infectious in terms of the primary diagnosis. Currently, we are looking – because the data allow that – at the secondary diagnosis too. But when a patient is taken to hospital for a myocardial infarction and he gets an infection, most of the data will refer to the infarction and not the infection. So the quality of the data on infections in the database may be relatively poor.

J. Vandenbroucke: I assume you have very few hospitalisations with infection being the primary reason.

Leufkens: Very few.

Van der Meer: I think the data really fit in with my idea about type-2 diabetes that the infectious problems are there, but they are not very much increased compared with the reference background of an ageing population. If you look at women of the age-groups at which you have looked, there is a high incidence of bacteruria which is largely asymptomatic, occasionally symptomatic. Thus, there may be many prescriptions written for the background population, and diabetes adds only a little to that. But that may not be the full explanation. I like the idea of Dr. Siem de Marie that one does not develop type-2 diabetes overnight. Often something happens, e.g. a patient develops symptoms compatible with a urinary-tract infection, goes to the doctor, and at that point in time the urine is examined, not only for leucocytes, but also for glucose, and you end up with two diagnoses at the same time. That may be the explanation for seeing what you saw by modelling the prescription data.

Kullberg: If you ask yourself what is special about cephalosporins and the quinolones, there are two things you are likely to find. First, the use of those drugs per os has increased tremendously over the past decade. So that is another argument for the exercise Jan Vandenbroucke suggests, to be very sure that things are well matched for the time of incidence. Another thing is that they are typically used as second-line therapies after the failure of another therapy. The question is, were these patients treated for recurrence of the same type of infection either before the diagnosis of diabetes had been made or after? Could that be part of the explanation, whereas the other patients had been being treated for another type of infection each time they had a new prescription?

Leufkens: To come back to your last point: I am not a clinician, but what I really found very surprising to see was that the recurrence rate was so high in these patients. At the tine there was for instance the Markov chain of, say, amoxycillin and then a quinolone. That transition was kind of predictive of a whole chain of quinolone prescriptions afterwards. So that sequence, as you were just saying, and those patients are not normal, because normally you could say they could have been treated by just one or two courses of an antibiotic, but now they started off the whole sequence and did not stop using antibiotics.

Kullberg: But since the quinolones and the cephalosporins are being used as last-resort agents, it is not strange that, if one has progressed to those antibiotics, the next prescription will be another broad-spectrum oral antibiotic. A third explanation might be that, if there is a difference in prescribers, it could be that diabetics are seen more often by clinicians who have a tendency towards prescribing more advanced drugs.

Leufkens: That fits in with the comment I made earlier, that the moment patients are diagnosed as being diabetic, most of them are treated by an internist or other specialist. Then they embark on a completely different route of prescription, involving specific antibiotics.

Kullberg: And there may even be an interaction, because if the internist has prescribed the quinolone, the GP may think that that is probably what he should have done in this case.

De Jongh: You said that a drug prescription induces more drug prescriptions. Could it be that actually making a diagnosis induces more diagnoses? Once diagnosed as a diabetic, you will be looked at more closely, and that will in general yield more diagnoses?

Leufkens: The answer should be, 'Of course, both'. The very contact between a physician and a patient will result in a prescription, but a physician, being aware that this patient has diabetes, having all the training, is even more inclined to write a prescription. Once diagnosed, patients will visit physicians at a higher rate. Thus, I think both explanations fit here: a higher likelihood of prescriptions after being diagnosed and also just because of more contacts.

Verbrugh: Thanks very much. I would like to spend just a few minutes not really on your topic but to reflect on the day. When we started out on this topic, we were wondering what we were getting into. My opinion has changed: I am not reluctant at all about modelling any more. Talking to people specialising in it, we have much to discuss; this last talk illustrated that nicely. I am rather enthusiastic about what we have learned today, and perhaps it will give another impulse for such work to be done in The Netherlands in contacts between mathematicians, modellers, strategists, epidemiologists and the infectious-disease community. But perhaps I am a bit too optimistic, and I would like to hear other comments.

J. Vandenbroucke: I made the suggestion to one of the modellers, Dr. de Boer, that maybe he should write a paper in defence of modelling, not just to counter my paper, which was in another context, but to explain why modelling is necessary, how you start with it, what you know intuitively, and also how you can meet with surprises. I also learned today that, even if you get surprises from models, you still should be able to explain them intuitively afterwards, because otherwise you won't believe them. As regards these considerations and also the similarity with experimental research – is an experiment more valid than a model, or can a model in some instances be more valid than an experiment? – I think that it might be important to confront not only infectious-disease physicians, but also general physicians, with these concepts. We also learned that the most important thing might be to make the model and to discuss your uncertainties. It is extremely important that physicians and researchers know that they should interact with model makers.

Boucher: I think what I have learned in the interaction is that you have data, maybe a hypothesis, you start to model it, and at some point you get a new hypothesis. Then the next phase is to actually test that hypothesis in your experiments and to see whether it fits. Today I actually saw only one phase, data and models, but nobody actually presented the test of a given model. To use models in the appropriate way is to go to different cycles, developing, testing them in an experimental setting, come back and refine your model, and then it really starts to become very useful. So it is the process of modelling and remodelling that counts. Just to come forward with an untested model may not be very helpful. A testing phase is needed to learn how valid a given model is.

Verbrugh: I think we did have some models that were extensively used in practice. I am looking at the Onchosim model. That was indeed also a model. Dr. Nagelkerke told us that you always have to work on your models, and basically what you are saying is that it is a process rather than a single result. I think Dr. Mirjam Kretszchmar also said exactly the same thing, that you basically are never finished with it. But it is something that can be directly evident or directly valuable for clinical practice. Those of us working in a clinic, I am sure, can use that technology to better streamline our intuitive thoughts and set limits where we should be called back and told, 'Listen, this cannot really be true.'

Levin: Somebody once said, 'I do not believe the data until they are confirmed by theory.' I do not think it is all that silly. I think there is a problem doing mathematical modelling. During my whole career we have done experiments and modelling. There is a problem when you are using mathematical modelling that there seems to be a different language. But we are using modelling all the time. Do you really think the Lac operon looks like a line with a Z, a Y, an O and an A, and a little Pacman? This is not the way it really looks of course. Does DNA really have different coloured planes across it? Those are models. We are continually using models. It is just that we are dealing with the problems of today, we are dealing with quantitative problems. Sure, the results should be intuitively clear, and should be explainable on intuitive grounds. But then sometimes the numbers really count. Knowing what the numbers are becomes critical, and for that you need the models. And I also refer to this point about testing. I sometimes see that we do experiments and that we really use models directly that generate the hypotheses. When you get the model to fit, then you stop under the assumption that you are correct, and that is the greatest danger. In a way, we may learn more when the model does not fit. There is a need for more collaboration. You asked how we get our questions. We get our questions by sitting and having dinner with you guys, and that is what I think really counts.

Verbrugh: Thank you very much.