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D E C I S I O N
of 15 March 2005

Case Number: T 0243/02 - 3.2.2

Application Number: 93923366.4

Publication Number: 0616540

IPC: A61M 1/16

Language of the proceedings: EN

Title of invention:
Hemodialysis monitoring for hemodialysis machines

Patentee:
Baxter International Inc.

Opponent:
Fresenius Care Deutschland GmbH

Headword:
-

Relevant legal provisions:
EPC Art. 56, 123(2)
EPC R. 57(a)

Keyword:
"Amendments - added subject-matter - yes (sixth auxiliary request)"
"Amendments - not occasioned by grounds for opposition (third and fourth auxiliary requests)"
"Inventive step - no (all further requests)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0243/02 - 3.2.2

D E C I S I O N
of the Technical Board of Appeal 3.2.2
of 15 March 2005

Appellant: (Patentee)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 6 February 2002 revoking European patent No. 0616540 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: T. K. H. Kriner
Members: M. G. Noël
M. B. Tardo-Dino

Summary of Facts and Submissions

I. European patent No. 0 616 540 was revoked by decision of the opposition division issued on 6 February 2002 on the ground of lack of inventive step of its subject-matter vis-à-vis the state of the art represented among other things by documents:

D1: US-A-4 244 787, and

D5: "Is Urea Kinetic Modelling an Appropriate tool for Guiding Ultrashort High-Flux Dialysis Therapy? by F. Lopot, University Hospital 2, Department of Internal Medicine, Praha-Strahor; Nephrol Dial Transplant Suppl. 3 (1991) 86 - 87.

II. The appellant (patentee) lodged on appeal against this decision by notice received on 28 February 2002 and filed a statement of grounds on 29 May 2002. The fee for appeal was paid on 1 March 2002.

III. Oral proceedings were held on 15 March 2005, at the end of which the requests of the parties were as follows:

The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted or, alternatively, on the basis of one of the auxiliary requests 1 to 4 filed with the letter dated 11 February 2005 or 5 to 7 filed during the oral proceedings.

The respondent (opponent) requested that the appeal be dismissed.

IV. The sets of claims according to the different requests each contain at least one independent apparatus claim and at least one independent method claim. Since the features of the independent method claims correspond strictly to those of the apparatus claims, only the latter are presented hereinafter. The different main apparatus claims read as follows:

Main request:

"An apparatus for monitoring in real time a hemodialysis treatment of a patient with a hemodialysis machine including a dialyzer and dialysate waste effluent removed from the dialyzer, the apparatus comprising:
a dialysate effluent constituent sensor (14) and means for separately coupling a plurality of separate fluid portions of the dialysate effluent to said constituent sensor during a dialysis treatment which depletes intracellular and extracellular pools of the constituent in the patient, the sensor being operable to generate a signal in response to the sensed dialysate effluent constituent; and
an analyzer (18) connected with the sensor (14) to receive said signal and determine from the signal, concentrations of said constituent in each of said dialysate effluent portions, the analyser (18) being operable to determine a dialysate effluent constituent concentration-time profile from said constituent concentration determinations;
characterised in that the analyser (18) is operable to carry out at least a two pool analysis of the profile by fitting said profile to a non-linear function that takes into account the degree of depletion of the

constituent from the extracellular and intracellular pools; and
to determine an indication of adequacy of said dialysis treatment from said analysis of the constituent concentration-time profile."

First auxiliary request:

"An apparatus for monitoring in real time a hemodialysis treatment of a patient with a hemodialysis machine including a dialyzer and dialysate waste effluent removed from the dialyzer, the apparatus comprising:
a dialysate effluent constituent sensor (14) for sensing urea or a constituent related to urea and means for separately coupling a plurality of separate fluid portions of the dialysate effluent to said constituent sensor during a dialysis treatment which depletes intracellular and extracellular pools of the urea or related constituent in the patient, the sensor being operable to generate a signal in response to the sensed dialysate effluent constituent; and
an analyzer (18) connected with the sensor (14) to receive said signal and determine from the signal, concentrations of said urea or related constituent in each of said dialysate effluent portions, the analyzer (18) being operable to determine a dialysate effluent constituent concentration-time profile from said constituent concentration determinations;
characterized in that the analyzer (18) is operable to carry out at least a two pool analysis of the profile by fitting said profile to a non-linear function that takes into account the degree of depletion of the urea

or related constituent from the extracellular and intracellular pools; and
to determine an indication of adequacy of said dialysis treatment from said analysis of the constituent concentration-time profile."

Second auxiliary request:

The main apparatus claim is formed of the preamble of the above apparatus claim according to the first auxiliary request and the following characterising portion:

"**characterised** in that the analyzer (18) is operable:
to carry out at least a two pool analysis of the profile by fitting said profile to a non-linear function that takes into account the degree of depletion of the urea or related constituent from the extracellular and intracellular pools;
to determine at least one of urea removal, KT/V, PCR and URR from the analysis; and
to determine an indication of adequacy of said dialysis treatment from said analysis of the constituent concentration-time profile."

Third and fourth auxiliary requests:

These requests contain several independent apparatus claims, claim 3 of the third auxiliary request and claim 1 of the fourth auxiliary request being identical to the apparatus claim according to the following fifth auxiliary request.

Fifth auxiliary request:

The main apparatus claim is formed of the preamble of the above apparatus claim according to the first auxiliary request and the following characterizing portion:

"**characterised** in that the analyzer (18) is operable to:
carry out at least a two pool analysis of the profile by fitting said profile to a non-linear function that takes into account the degree of depletion of the urea or related constituent from the extracellular and intracellular pools;
to project a final urea concentration measurement for the completion of the dialysis treatment from said analysis at a point in time significantly prior to completing said dialysis treatment and to project at least one of urea removal, KT/V, URR, PCR and a solute removal index (SRI) from said projected final urea concentration value; and
to determine an indication of adequacy of said dialysis treatment from said analysis of the constituent concentration-time profile."

Sixth auxiliary request:

The main apparatus claim is formed of the preamble of the above apparatus claim according to the first auxiliary request and the following characterising portion:

"**characterised** in that the analyzer (18) is operable to:
carry out at least a two pool analysis of the profile by fitting said profile to a non-linear function that takes into account the degree of depletion of the urea or related constituent from the extracellular and intracellular pools;
to project a final KT/V for the completion of the dialysis treatment from said analysis at a point in time significantly prior to completing said dialysis treatment; and
to determine an indication of adequacy of said dialysis treatment from said analysis of the constituent concentration-time profile and to trouble shoot the hemodialysis treatment, if the final projected KT/V result is too low."

Seventh auxiliary request:

The main apparatus claim is formed of the content of the above apparatus claim according to the first auxiliary request and the following feature added to the end of the claim:

"and in that the apparatus including means for obtaining an equilibrated urea concentration measurement prior to starting the dialysis treatment, or after completing the dialysis treatment, the analyzer (18) being operable to determine a solute removal index (SRI) from said equilibrated concentration measurement and said analysis."

V. At the oral proceedings the parties argued as follows:

(i) the appellant

Document D1 disclosed an apparatus for determining serum concentrates of metabolites, in which dialysate concentrations were sensed and converted to serum concentrations for evaluation of the therapy. For urea, D1 only observed one-pool modelling and analysis. A two-pool modelling was also contemplated, but only in relation to phosphate removal monitoring. As to urea, control of therapy was achieved by calculating the total mass transferred and not, like the invention, by carrying out a two-pool analysis of the constituent concentration-time profile and by fitting said profile to a non-linear function that took account of the two-pool behaviour and kinetics of the constituent.

Document D5 set out a comparison between single-pool and two-pool modelling for urea kinetics, but was restricted to a high-flux dialysis therapy. Moreover, urea concentration were provided on the blood side and not directly derived from the dialysate fluid. A person skilled in the art thus would not have arrived at the subject-matter of claim 1 of the main request by combining the teaching of documents D1 and D5. The subject-matter of claim 1, therefore, was not obvious.

The claims according to the first and second auxiliary requests specified that the apparatus

was specifically intended for the monitoring of urea and for the determination of urea removal or other parameters indicative of the dialysis adequacy. These features further distinguished the claimed subject-matter from the state of the art.

The third and fourth auxiliary requests contained various aspects of the invention set out in different independent claims, each specifying features regarded as essential vis-à-vis the state of the art.

The fifth auxiliary request specified successive projections, made at significant times of the dialysis, of the final urea concentration and of the urea removal or other adequacy parameters. Although in D1 urea concentration measurements were made during the dialysis, these data were not used to predict the performance of the dialysis before the end of the treatment. In particular, D1 did not teach how the urea levels were extrapolated for achieving pre- and post-dialysis body levels, wereas claim 1 in suit specified that the projections of the urea concentration were obtained from the two-pool analysis of the profile referred to in the preceding feature.

The features added to the claims according to the sixth auxiliary request, concerning trouble shooting the hemodialysis treatment in dependence of the projected value of KT/V, were drawn up from the description and, therefore, fairly supported.

The seventh auxiliary request specified the balance of urea concentration to be obtained in the fluids prior to starting the dialysis treatment. This feature was not disclosed by the prior art documents, either.

(ii) the respondent

Document D1 disclosed that urea measurements could be validly made directly on the dialysate side because the blood constituent concentrations were directly reflected by their dialysate concentrations. D1 further disclosed that a dialysate constituent concentration-time profile was established and could be used for analysing the adequacy of the dialysis treatment by extrapolation to zero time and to the end of dialysis. For urea, however, only one-pool modelling was concerned, although limitations were known for constituents which were diffusing in more than one body compartment. The subject-matter of claim 1, therefore, only differed by carrying out at least a two-pool analysis of said profile.

Also document D5 reported that limitations were disclosed for urea when using a conventional single-pool urea kinetic modelling (UKM) and proposed instead to use a more realistic two-pool analysis of urea concentration profiles for estimating the adequacy of short dialysis treatments. The skilled person, therefore, would inevitably be prompted to conduct a two-pool analysis of the profile also from constituents sampled on the dialysate side of the dialyser, so

as to get a better indication of adequacy. Consequently the subject-matter of claim 1 according to the main request did not imply any inventive step having regard to the teachings of D1 and D5.

The amendments made to the claims according to the various auxiliary requests were all known *per se* from the cited documents, taking account of the general and functional wording of these claims. In particular, urea analysis was specifically considered in document D1 for determinating dialysate urea levels during dialysis and, hence, the final urea concentration, the urea removal or a dietary index by means of extrapolations to zero time and to the end of dialysis. Since the features introduced in the different requests failed to distinguish the claimed subject-matter over the prior art, the requirement of inventive step was still not met.

Reasons for the Decision

1. The appeal is admissible.

2. *Formal aspects (third, fourth and sixth auxiliary requests)*

2.1 The third and fourth auxiliary requests which were filed in reply to the Board's communication dated 15 December 2004, include each at least two independent claims in the same category (apparatus and method), while the claims as granted include only a single

independent claim in this category. The filing of several independent apparatus and method claims instead of a single independent claim in each category was neither motivated by a ground for opposition, nor to overcome the obviousness objection of the Board. Rather, they give rise to further formal objections of clarity and conciseness under Article 84 and Rule 29 EPC. Therefore, these requests are not admissible with respect to the provisions of Rule 57(a) EPC.

2.2 As to the sixth auxiliary request, the Board remarks that the feature added to the end of the claim ("and to trouble shoot the hemodialysis treatment") is conditional on the value of the projected adequacy parameter ("if the final projected KT/V result is too low"). According to the patent description (page 8, lines 33 to 36), however, the hemodialysis treatment is trouble shooted by using a so-called mid-treatment projection, which is referred to in the previous sentence as being the projection of the final urea concentration. But since said projection of the final urea concentration measurement was also deleted from the claim according to said auxiliary request, the new wording results in introducing subject-matter extending beyond the content of the application as originally filed, which is contrary to the requirements of Article 123(2) EPC.

3. *Inventive step*

3.1 Main request

3.1.1 Document D1 is considered by the Board as the closest prior art document. Following the terminology used in

claim 1, D1 discloses (Figure 1) an apparatus for monitoring in real time a hemodialysis treatment of a patient with a hemodialysis machine including a dialyser and dialysate waste effluent 11 removed from the dialyser. The apparatus further comprises a ion-selective electrode or sensor 29 for sensing a dialysate effluent constituent (urea or phosphate) and means 18, 25 for sampling fluid portions of the dialysate effluent during the dialysis. The sensor is operable to generate a signal in response to the sensed dialysate effluent constituent, said signal being received by an analyser for determining the concentration of the constituent in each sample (column 1, line 67 to column 2, line 4; column 3, lines 62 to 66 and column 4, lines 1 to 6). From said constituent concentration determinations, a dialysate effluent constituent concentration-time profile can be determined (Figures 3, 5 and 8; column 5, lines 63 to 64).

An object of the system described in D1 is to provide an apparatus for monitoring the progress of the dialysis therapy without the necessity of blood sampling, i.e. by controlling the concentration of the constituents on the dialysate side and in particular such parameters as urea removal, the ratio KT/V or the protein catabolic rate (PCR), which are indicative of the adequacy of the treatment (column 1, lines 48 to 50; column 2, lines 9 to 12 and column 5, lines 63 to 67). With the view to hold the loss of blood to a minimum with end stage renal patients, in D1 the concentrations of the constituents are monitored and analyzed in real time without withdrawing blood from the patient, by directly sampling and analyzing the

dialysate solution which is equilibrated with the blood via the hemodialyser (column 1, lines 11 to 20; column 2, lines 12 to 17 and column 7, lines 26 to 31). This provides for improved control of the therapy during the treatment.

In Figures 1 and 5 dialysate concentration measurements are made and represented versus time for urea, which is supposed to exhibit a single-pool behaviour (column 3, lines 62 to 66 and column 5, lines 63 to 64). Thus, contrary to the assertions of the appellant, in document D1 the measurements are made on the dialysate side and not on the blood side, as is already apparent from the title of this document. Keeping in mind the close relationship existing between the concentrations on both sides of the dialyser once equilibrated (column 4, lines 49 to 57), the values of the dialysate validly reflect the serum concentrations for monitoring purposes. It is true that dialysate measurements are converted to serum concentrations in D1. However, this conversion only assists in comparing said serum concentrations obtained from the dialysate measurements with other concentrations obtained from blood samples taken during the dialysis treatment and analyzed by an autoanalyser for testing the reliability of the indirect method described in D1. But for evaluation of the therapy the serum concentration itself is not needed (column 5, lines 8 to 9). The above clinical procedure is described in detail in column 4, lines 33 to 34 and appears to be satisfactory as to accuracy. Figure 6 represents the blood concentration resulting from the conversion of the dialysate measurements shown in Figure 5, whereas the results of the above comparison are summarized in table I (column 6, lines 1

to 28) and confirm the reliability of the indirect method.

The existence of a secondary pool is also referred to in D1, but in relation to the removal of phosphate, the concentrations of which on the blood side and on the dialsysate side are illustrated in Figures 7 and 8, respectively. Since the nature of the constituent is not specified in claim 1 according to the main request, the passage in column 7, lines 3 to 25 of D1 is relevant as well. However, as recited in the quoted passage, the non-linearity of the graph of Figure 7 does not allow to use equation (3) to estimate the total removal of inorganic phosphorus. Instead, an estimate is provided by manual integration of the urea under the dialysate concentration-time profile shown in Figure 8, which is certainly a process different from the process resulting from the characterising features of claim 1 in suit.

3.1.2 The subject-matter of claim 1, therefore, only differs from that which is disclosed in D1 by the characterising feature according to which the two-pool analysis of the profile is carried out by fitting said profile to a non-linear function that takes into account the degree of depletion of the constituent from the extracellular and intracellular pools.

On the basis of this distinguishing feature, the objective problem underlying the present patent is to provide an apparatus for accurately assessing either the dietary compliance or the adequacy of the hemodialysis treatment in a non-invasive, real time

monitoring method that takes account of the two-pool nature of urea removal.

Although the two-pool behaviour for urea was also generally known from the skilled person, document D1 simply does not take advantage of this characteristic for urea.

3.1.3 Document D5 points directly away from monitoring dialysis adequacy by means of single-pool urea kinetic modelling (UKM), because this conventional technique has limitations that restricts its validity and usability. For treatments with dialysis time less than three hours, which are of the same order as those contemplated in the present patent, this conventional technique leads, among others, to an overestimated protein catabolic rate (PCR) by as much as 20%, due to the non-accounted post-dialysis rebound (Figure 1) and the urea concentration gradient between the extracellular and the intracellular compartments.

To investigate this phenomenon a computational analysis of urea concentration curves generated by UKM and by a more realistic two-pool model was made (cf. Abstract, page 86 and right column, third paragraph). Figure 2 of D5 shows the time course of blood urea concentration during dialysis, as calculated from single-pool UKM equations (curve 1) and from a two-pool model (curve 2). The two curves intersect at point X which reflects the concentration equilibrium in the two compartments as a consequence of increasing diffusion and urea removal with time from the intracellular space, as explained in the present patent in relation to Figures 3 and 4 and the inflection point 116. The

point X is situated at 3 - 4 h dialysis time instead of about half an hour in the patent. But as explained in D5 (page 87, right column) the location of the point X is a function of the intercompartmental mass transfer coefficient for urea, the patient's distribution volume (patient's size) and the dialyser clearance, i.e. of the specific application contemplated. Therefore, the analysis principles are the same in D5 as in the present patent.

Taking account of the general and functional wording of the distinguishing feature of claim 1 over D1, the skilled person is thus taught by document D5 and in particular by Figure 2 of this document, that a two-pool analysis of the constituent concentration-time profile can be conducted by fitting said profile to a non-linear function that takes account of the degree of depletion of the constituent from the extracellular and intracellular pools. In this respect it is irrelevant that in D5 urea concentrations are measured on the blood side, since the relationship with the dialysate concentrations and the reliability of measurements made on the dialysate side have already been established by document D1 which is regarded as the closest prior art.

The skilled person, therefore, will be induced to combine these documents to arrive at the subject-matter of claim 1. As a consequence, the Board is convinced that the subject-matter of claim 1 according to the main request does not involve as inventive step within the meaning of Article 56 EPC.

3.2 First auxiliary request

As it results from the foregoing, the continuous monitoring of urea levels from the dialysate effluent is disclosed in document D1, in particular in relation to the description of Figures 1 and 5. Also document D5 is focused on the comparison between one-pool and two-pool modelling for urea. Therefore, the specification in claim 1 according to the first auxiliary request that the effluent constituent may be urea does not involve any inventive step.

3.3 Second auxiliary request

In document D1 the evaluation of the therapy is principally based on the determination of the total mass of the constituent transferred, which can be obtained from the formula given in column 5, line 15. For urea a simplified mass transfer equation is used to evaluate the urea removed from the patient (see column 5, lines 56 to 58; column 6, lines 29 to 31 and Table II). Also the ratio K/V can be derived from Figures 5 by the slope of the linear representation of the dialysate urea concentration versus time (column 5, lines 63 to 67) and hence the value KT/V which is defined in the contested patent as a preferred parameter for measuring dialysis adequacy (see patent, page 2, lines 39 to 41 and page 3, lines 10 to 11).

Consequently, the feature added to claim 1 according to the second auxiliary request, that the two-pool analysis is carried out to determine at least one of urea removal, KT/V, PCR and URR from the analysis, is also known from document D1. Therefore, the

subject-matter of this claim does not involve an inventive step, either.

3.4 Fifth auxiliary request

By determining, in document D1, urea levels during dialysis, precise estimates to pre- and post-dialysis body levels of urea can be provided (column 2, lines 7 to 9). Said another way, by either continuous or intermittent measurement of the dialysate effluent it is possible to determine not only the instantaneous serum levels (via equations (1) and (2) - see column 5, lines 4 to 6) but also pre- and post-dialysis levels by extrapolation to zero time and to the end of the dialysis. From these levels, protein catabolic rates (PCR) can, in turn, be projected (column 2, lines 9 to 10), using the well-known relationships described by Gotch and Sargent (column 6, lines 54 to 61).

It must be recalled here that PCR is a measure of protein intake and a determinant of need for dialysis, which is identified in the present patent as the dietary compliance (page 3, lines 23 to 26 and page 4, lines 14 to 16). Since moreover these projections are made during the dialysis, they are necessarily made "at a point in time prior to completing said dialysis treatment". Besides, it is also for avoiding significant overestimation of the PCR factor that a two-pool modelling analysis is recommended for urea in document D5.

Thus, again, having regard to the vague and functional wording used in the features incorporated in claim 1 according to the fifth auxiliary request, it is the

Board's opinion that its subject-matter still cannot be distinguished from the disclosure of document D1. In both cases a final urea concentration value is projected before the end of the dialysis treatment so as to subsequently project therefrom at least one of the above mentioned adequacy or dietary parameters. Therefore, the subject-matter of this claim is also suggested by the combination of document D1 and D5.

3.5 Seventh auxiliary request

Also in document D1 an equilibrated urea concentration measurement between blood and dialysate is obtained prior to starting the dialysis treatment (column 1, lines 15 to 20 and lines 51 to 54). As to the determination of a solute removal index (SRI) which, according to the present patent (page 7, lines 53 to 54) represents the fraction of solute (urea) that has been removed from the total body stores by hemodialysis, the added feature is expressed so generally that it does not distinguish the claimed subject-matter from the disclosure of documents D1 or D5, the aims of which are also to remove urea, partly or in totality, from the body pools.

It results therefrom that the subject-matter of claim 1 according to the seventh auxiliary request does not imply any inventive step vis-à-vis the teachings of document D1 and D5.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

V. Commare T. Kriner