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A STUDY TO EVALUATE INTER INDIVIDUAL VARIATIONS IN CAUSAL ASSESSMENT USING NARANJO AND WORLD HEALTH ORGANIZATION UPPSALLA MONITORING CENTRE (WHO-UMC), CAUSALITY SCALE

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INTRODUCTION

Pharmacovigilance has come up as an important subject in last few decades. The need for adverse drug reaction reporting and sharing the information came into light after the thalidomide crisis in sixties.[1] Thalidomide was a drug approved in fifties as an antiemetic for morning sickness, in first trimester of pregnancy.[1] By the time teratogenic potential of the drug came into light thousands of newborns were affected by this drug by developing phaecomaelia.[1] Since then, countries all over the world realized importance of adverse drug reaction reporting and further getting causal assessment of the drug reaction relationship.[2] United States of America(USA), European Union(EU) and many other countries developed their own system of reporting and causal assessment.[2] There are different ways of doing a causal assessment for a reported adverse drug reaction (ADR). We have global introspection which is based on clinical judgment, probalistic analysis and algorithms.[2] Different algorithms uses a defined format to draw a conclusion, we have World Health Organization (WHO) method, Naranjo scale, Karsh-lasagna, Roussel-uclaf, Imputability and many more.[2] Many countries are following a common programme conducted by WHO, having its centre in Uppsalla, Sweden called Uppsalla Monitoring Center (UMC).[3]

Main reason for having a systemized Pharmacovigilance programme is to detect a possibility of a new adverse reaction of a drug which is not documented in past literature.[4] This further depends on assessor who is doing a casual assessment using same scale used in that particular county or region.[5] As different monitoring centre will have different group off assessors doing casual assessment. Therefore proper understanding, of the scale being used is of utter importance. Different doctors will have different level of understanding and there would be a possibility of inter individual variation in coming to final conclusion.[6] Inter individual variation can tell us about consistency of a scale. More the inter indifference, lesser the consistency of scale, because of lesser level of understanding by all assessors, as every human is different in their logical analysis.[7]

MATERIAL AND METHOD

After duly taking ethical committee clearance a small observational cross sectional study was conducted. 100 medical students participated in the study, they were told about the study and what they were expected to do. Subsequently informed consent were taken from all of them.

We used two scales for causality assessment, firstly WHO-UMC causality scale and secondly Naranjo scale, given below:

Table 1: WHO-UMC causality scale.[8]

Casualty term	Assessment Criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs. • Response to withdrawal plausible (pharmacologically, pathologically). • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). • Rechallenge satisfactory, if necessary.
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Unlikely to be attributed to disease or other drugs. • Response to withdrawal clinically reasonable. • Rechallenge not required.
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Could also be explained by disease or other drugs. • Information on drug withdrawal may be lacking or unclear.
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). • Disease or other drugs provide plausible explanations.
Conditional/ Unclassified	• Event or laboratory test abnormality. • More data for proper assessment needed, or • Additional data under examination.
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction. • Cannot be judged because information is insufficient or contradictory. • Data cannot be supplemented or verified.

Table 2: Naranjo Scale.[9]

1. Are there previous conclusive reports on this reaction?	Yes (+1) No (0) Do not know or not done (0)
2. Did the adverse event appear after the suspected drug was given?	Yes (+2) No (-1) Do not know or not done (0)
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes (+1) No (0) Do not know or not done (0)
4. Did the adverse reaction appear when the drug was readministered?	Yes (+2) No (-1) Do not know or not done (0)
5. Are there alternative causes that could have caused the reaction?	Yes (-1) No (+2) Do not know or not done (0)
6. Did the reaction reappear when a placebo was given?	Yes (-1) No (+1) Do not know or not done (0)
7. Was the drug detected in any body fluid in toxic concentrations?	Yes (+1) No (0) Do not know or not done (0)
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Yes (+1) No (0) Do not know or not done (0)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes (+1) No (0) Do not know or not done (0)

Naranjo Scoring
> 9 = definite ADR
5-8 = probable ADR
1-4 = possible ADR
0 = doubtful ADR

These two scales were taken as they are the most commonly used scale and are simple to understand as we had to teach them to the medical students. All 100 medical students were taught how to use these two scales for casualty assessment. After cross checking whether each and every one understood these scales by personal interaction and examples, they were divided into two equal groups of fifty students each.

First group were given 10 Adverse reactions forms previously reported and were told to do casualty assessment individually using WHO-UMC scale, whereas second group were also given same 10 Adverse drug reactions reported and were told to do the casualty assessment using Naranjo scale.

After their results were collected we crossed over the assessment scales. Now new set of 10 Adverse drug reactions reported previously were given to first group who now had to use Naranjo scale to do casualty assessment whereas for the same adverse drug reactions second group had to do casualty assessment using WHO-UMC scale.

RESULTS

Results are tabulated as below:

Table 3: Causality Assessment done using WHO-UMC scale for first set of 10 adverse drug reactions by first 50 students.

ADR	1	2	3	4	5	6	7	8	9	10	Avg (%)
Probable	34	30	29	27	31	25	29	22	24	23	54.8
possible	12	15	14	21	18	24	18	18	16	18	34.8
Unlikely	4	5	7	2	1	1	3	10	10	9	10.4

Table 4: Causality Assessment done using Naranjo scale for first set 10 adverse drug reactions by first 50 students.

ADR	1	2	3	4	5	6	7	8	9	10	Avg(%)
Probable	44	43	40	41	47	39	37	42	43	46	84.4
possible	6	7	10	9	3	11	13	8	7	4	15.6

Table 5: Causality Assessment done using WHO-UMC scale for second set of 10 adverse drug reactions by second 50 students.

ADR	1	2	3	4	5	6	7	8	9	10	Avg (%)
Probable	23	30	28	22	24	20	26	33	29	23	51.6
possible	24	11	12	26	18	18	9	10	17	20	33
Unlikely	3	9	10	4	8	12	15	7	4	7	15.4

Table 6: Causality Assessment done using Naranjo scale for second set of 10 adverse drug reactions by second 50 students.

ADR	1	2	3	4	5	6	7	8	9	10	Avg(%)
Probable	43	38	42	43	44	42	41	39	37	45	82.8
possible	7	12	8	7	6	8	9	11	13	5	17.2

DISCUSSION

As we know there are different ways to do casual assessment of adverse drug reactions, one of the commonest one out of them are using WHO-UMC probability scale and Naranjo scale. As we saw consistency in getting results from doing Casualty assessment using WHO-UMC scale for both set of 10 adverse drug reactions given to both populations was less as compared to Naranjo scale. Both populations showed more consistency in deriving similar results after using Naranjo Scale for casualty assessment of both sets of 10 adverse drug reactions each. When WHO-UMC scale was used students came into three different type of results probable, possible, unlikely, having average of 54.8% for probable, 34.8% for possible and 10.4% for unlikely, for first set of 10 ADRs. On the other hand after using Naranjo scale students concluded mainly into two probable and possible, with an average of 84.4% in probable and 15.6% in possible on same. On other hand, for second set of 10 ADRs using WHO-UMC scale, have average of 51.6% for probable, 33% for possible and 15.4% for unlikely and using Naranjo scale, it had an average of 82.8% in probable and 17.2% in possible . On other hand , for second set of 10 ADRs, unlikely have average of 51.6% for probable, 33% for possible and 15.4% for unlikely, using Naranjo I had an average of 82.8% in probable and 17.2% in possible. This difference may be because for WHO-UMC scale based more on the understanding and logical analysis about the scale which may be different for different individuals. On other hand Naranjo scale is based on simple scoring with three straight answers, yes , no or I don't know. This has lesser chances of inter individual difference in coming to a conclusion for casualty assessment of an adverse drug reaction.

CONCLUSION

This study was not based on proving any scale or method for casual assessment to be superior than others. We took two commonly used scales, just to see which scale is more consistent and can be easily understood and used by average population. We came into conclusion that naranjo scale was more consistent and easy to understand as compared to WHO-UMC scale, and hence having lesser inter individual differences.

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