Br. J. Cancer (1992), **66**, Suppl. XIX, S42-S45

Autonomic changes during cancer chemotherapy induced nausea and emesis

G.R. Morrow, C. Angel & B. Dubeshter

University of Rochester Cancer Centre, University of Rochester School of Medicine and Dentistry, New York, USA.

Summary Certain autonomic variables have been shown to be responsive to motion induced nausea and vomiting. Here we report preliminary data on changes in heart rate, blood volume pulse, pallor and skin temperature assessed during a one hour period at baseline, a one hour period of peak nausea, and a one hour period of emesis in five female patients receiving identical cancer chemotherapy and antiemetic drugs according to a common protocol. Examination of coefficients of variation showed that heart rate and face temperature were more stable measures across each of the three time periods than blood volume pulse and pallor. Furthermore, the four measures were found to be more variable during times of emesis than times of nausea.

The four measures were shown to be responsive to patient reported nausea and vomiting. Temperature and pallor showed a linear change from baseline to nausea to vomiting. Heart rate and blood volume pulse significantly decreased from baseline time during nausea and then significantly increased from a time of nausea to during emesis. Variations in the time course of each variable change during nausea supported a view that nausea may be more related to a rebound of parasympathetic activity than a slow decrease of sympathetic activity.

Replication with larger samples is needed. Examination of the nausea and vomiting of pregnancy, general anaesthesia or different chemotherapeutic agents could help explore whether results reported here are singular or representative of a more generalisable autonomic response associated with patient reported nausea.

Nausea is a common, unpleasant, and subjective response to excessive motion, toxins and cancer treatment through chemotherapy drugs. An alternative frame of measurement could promote research on individual subjective symptom expression and systematic investigation of etiologic insights that could lead to better control (Morrow, 1984; Redd *et al.*, 1991; Morrow, *et al.*, 1991). Here potential relationships between measures of sympathetic/parasympathetic autonomic nervous system activity and chemotherapy induced nausea and vomiting are reported.

Subjects and methods

Five females treated on the same inpatient hospital unit for ovarian cancer provided informed consent for the study. All received identical chemotherapy and antiemetic drugs according to a common protocol.

Measures

Choice of the autonomic nervous system variables of heart rate, blood volume pulse, pallor, and skin temperature was based on their theoretical importance, their ease of measurement, their representation of different aspects of the autonomic nervous system, and the availability of comparison data in the motion induced nausea literature (Money, 1970; Harding, 1990; Davis *et al.*, 1986; Cowings *et al.*, 1990).

Changes in face colour have long been associated with nausea in man. Phrases such as 'pasty white' and 'turning green' are parts of common speech. Early studies by NASA that examined changes in face colour for subjects being put through nausea-inducing motion in a rotating chair showed that it was extremely difficult to visually calibrate and rate skin colour reliably.

Pallor was measured by an infrared transmitter-receiver operating at 940 Nm (Oman & Cook, 1983). This frequency is transparent to skin melanin and therefore permits operation irrespective of pigmentation. The pallor detector is an optical transducer approximately 0.5 cm on a side, with a gallium arsenic light admitting diode transmitter and a silicone photo-diode detector with a red filter. The diode detects backscatter radiation reflected off hemoglobin concentration within the dermal circulation. Skin heating effects are negligible with the low current used to power the LED. Output is identified by pulsing at 250 Hz to eliminate stray input to the detector from external sources such as walking in and out of sunlight or rooms with different levels of illumination such as a patient's hospital room and bathroom. Values are linear voltage changes from a zero value baseline.

Research with drug-induced nausea has shown an inverse relationship between heart rate and self reported nausea. The possibility of an association between heart rate changes and experienced nausea may best be explained by reasoning that parasympathetic autonomic stimulation of the gut results in increased peristalsis while parasympathetic stimulation of the heart has been found to result in a decreased heart rate (Guyton, 1976). Innervation from the parasympathetic system of both heart and gut is largely by the vagus nerve. Given the common neurologic pathway, it is feasible that the subject who has experienced nausea might also show a decrease in heart rate since both can result from common parasympathetic stimulation. Heart rate change also depends on postural differences, which lead to a change in sympathetic/parasympathetic balance of heart rate.

Blood volume pulse (BVP) and heart rate were electronically processed as the oscillatory component of the pallor signal. As BVP is correlated with subject heart beat, it was electronically separated from the pallor signal with a 40 Db/decade band passed filter set at 0.5 to 2.5 Hz. This corresponds to heart rates of 30 to 150 bpm. BVP was reported in mV corresponding to the average amplitude of the measured signal.

A reduction in skin temperature has been associated with motion induced nausea. Cancer patients frequently report sensations of temperature changes when being treated with chemotherapy drugs. It is not uncommon, for example, to have patients want blankets or heavy sweaters in chemotherapy treatment rooms.

Skin temperature was measured using a small thermistor bead mounted in a separate plastic housing attached to the optical transducer housing with fine flexible wires to minimise mechanical compression of the micro-vessels inside the der-

Correspondence: G.R. Morrow, Behavioral Medicine Unit, University of Rochester Cancer Center, 601 Elmwood Ave., Box 704, Rochester, NY 14642, USA.

mal layer and reduce potential artifactual pallor due to skin motion. Time constant on the thermistor was 10 s. The instrument is responsive to skin temperatures over the range 32–42°C with accuracy of ± 0.2°C.

The temperature and pallor detection units were attached to subjects cheeks with double stick transparent tape. Data were recorded on a medilog MR-10 system. A timing pulse was placed on a separate channel to permit phase-lock processing of signal playback. Playback was accomplished on a Research Instrumentation Associates data retrieval system Model 10-200-1. Potential drift in the detector was assessed through the use of a Delrain block of known reflectivity. No discernible drift in the instrument detector was found over the time of the experiment.

Results

Patterns of change

Analyses used data from three, 60 min periods: (i) baseline, immediately prior to the administration to any chemotherapy drug; (ii) nausea, immediately prior to the patients' first emetic episode; and (iii) vomiting, following the first emetic episode. All patients reported nausea during the 60 min prior to their first emetic episode and continued to experience emesis during the one hour following their first emetic episode.

Mean values of the first 30 s of data for successive 5 min episodes of each one hour assessment period were calculated (Cowings *et al.*, 1986). An analysis of variance model followed by *t*-tests corrected by the Bonforoni procedure was applied to the data. Since pallor baseline was given as a zero value, this was considered the more appropriate statistical procedure.

Figure 1 presents mean (± SEM) values of temperature, blood volume pulse, pallor and heart rate for each of the three assessment periods. Face temperature was found to be different at the three assessment times ($F_{2,33} = 34.8$; $P < .01$). Values during nausea were found to be significantly lower than baseline ($t = 4.2$; $P < .01$) and significantly higher than during emesis ($t = 3.7$; $P < 0.01$).

Pallor during nausea showed a similar linear pattern to that of temperature. Significant differences were found among the three periods ($F_{2,33} = 50.9$; $P < .01$). A significant increase in pallor from baseline to time of nausea was found ($t = 8.3$: $P < .01$). A further increase was found during the time of emesis ($t = 5.2$; $P < .01$).

Blood volume pulse and heart rate responses showed a pattern different from temperature and pallor. Blood volume pulse was found to decrease significantly from baseline during the time of nausea and to increase significantly during a time of emesis. Blood volume pulse mean values were statistically different at the three times ($F_{2,33} = 7.9$; $P < .01$). A significant decrease was found from baseline to time of peak nausea ($t = 2.1$, $P < .05$) while a significant increase was found between nausea and time of emesis ($t = 3.7$; $P < .01$).

A pattern similar to blood volume pulse was found for heart rate. Overall, the three times were significantly different ($F_{2,33} = 67.9$; $P < .01$). A significant decrease from baseline was found during time of nausea ($t = 2.8$; $P < .05$). A significant increase was found between time of nausea and time of emesis ($t = 3.2$; $P < .01$). However, there was not a significant difference between the heart rate during time of emesis compared with baseline values ($t = 0.9$; $P > .05$).

Stability of measures

The stability of the measures during each of the sampled periods were examined by constructing the coefficient of variation (Colton, 1974). This summary statistic is the standard deviation of a measure divided by its mean. The lower the coefficient of variation, the more stable the measure. Values are shown in Table I for each of the three time

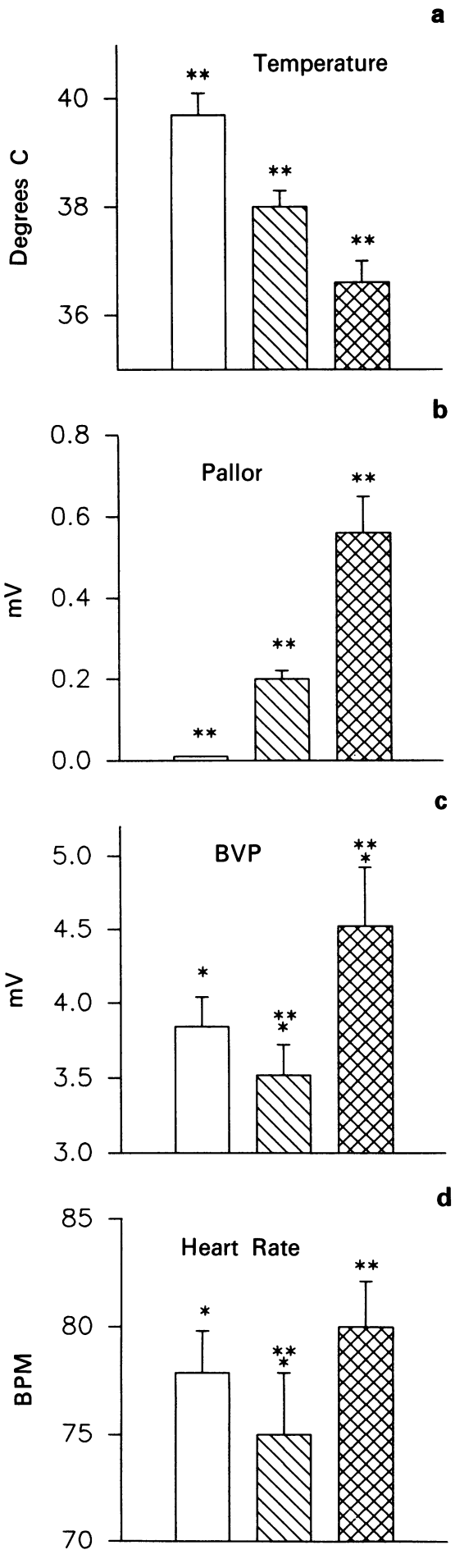

Figure 1 Mean values (±SEM) of temperature **a**, pallor **b**, blood volume pulse (BVP) **c**, and heart rate **d**, for each of three assessment periods: $*P < 0.05$; $**P < .01$. Pre Chemo □; nausea ▨; emesis ▩.

Table I The stability of measures during each sampled period: coefficient of variation

Measure	*Period* *Baseline*	*Nausea*	*Emesis*
Temperature	.01	.01	.01
Pallor	.01	.10	.16
Blood volume pulse	.05	.06	.09
Heart rate	.02	.04	.03

periods by each of the four measures. Heart rate and face temperature showed more stable measures across each of the three time periods than did blood volume pulse and pallor. Generally, the four measures were found to be more variable during emesis than during nausea.

Sympathetic/parasympathetic shifts

Previous studies with motion induced nausea have shown both sympathetic and parasympathetic changes. Cowlings has hypothesised that motion induced nausea is a phenomenon of parasympathetic rebound (Cowlings *et al.*, 1986). She theorises that the nausea associated with motion sickness is a concomitant of a large magnitude parasympathetic reaction in response to intense sympathetic activity. This mechanism is thought to be involved in other conditions such as vasovagal syncope and migraine headache (Graham *et al.*, 1961; Sakai & Myers, 1978). Such a hypothesis would predict that there would be a shift in the magnitude or predominance of primarily sympathetic *vs* parasympathetic variables as nausea became more intense or as vomiting developed. Visual inspection of the time course of each of the variables during the one hour nausea period prior to the first emetic episode showed that each reached a maximum value and then decreased during the time period.

The possibility that there was shift from sympathetic to parasympathetic activity during this time was examined through analysing when each of the four variables reached a maximum value. The time during nausea when each of the variables reached a maximum value is shown in Figure 2. The mean value and 95% confidence interval for the time when the value reached its maximum prior to emesis are presented.

An analysis of variance model on 1 min mean values showed different times of peak occurrence. Temperature had a maximum value at 49 min prior to the first emetic episode and then decreased. Pallor showed a bi-phasic change: maximum pallor (sympathetic dominance) was seen at approximately 40 min prior to emesis and maximum blush or minimum pallor (predominantly parasympathetic) at 15 min prior to an emetic episode. Blood volume pulse showed a maximum at approximately 23 min before decreasing while heart rate was the last of the variables to reach its maximum showing a maximum value at approximately 22 min prior to the first emetic episode with a steady reduction in heart rate until the time of emesis.

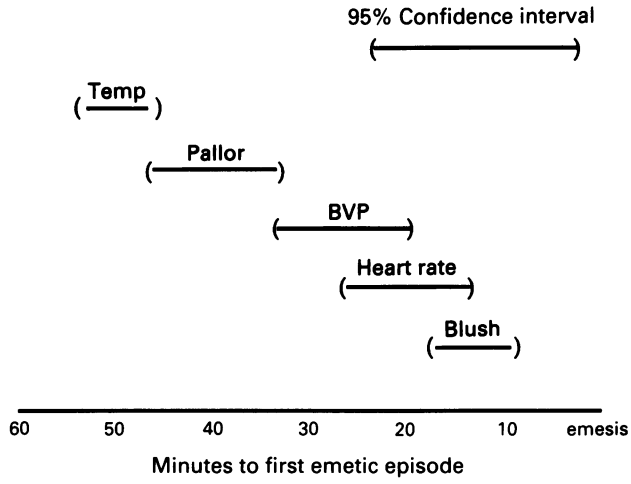

Figure 2 The time during the period of nausea and prior to emesis when each of the variables reached a maximum value.

Discussion

There is an emerging view that nausea may involve multiple inputs from the vestibular system, cortical areas of the brain and other visceral and autonomic inputs to a final common pathway. If it is assumed that one of the principal inputs to chemotherapy induced side effects is through the chemoreceptor trigger zone, this input effects its change at a different rate than the vestibular system (Oman, 1990; Morrow, 1985). There is the likelihood also of cross-linking between some of the systems. We have shown that patients with a susceptibility to motion sickness report greater nausea and emesis to the same chemotherapy drugs than patients who do not (Morrow, 1985). There thus may be different strengths of input that predominate for different types of nausea inducing stimuli.

The pattern of changes in heart rate, blood volume pulse and temperature were similar to those reported in motion induced nausea (Cowings *et al.*, 1986). This supports a view of a common final mechanism or a mechanism involving a final common pathway in the expression of nausea to these two challenges.

Given the small sample size and given the relative lack of comparative data from chemotherapy induced nausea, these data should best be considered suggestive rather than confirmatory. Replication with larger sample sizes is needed.

Changes in heart rate were found to be different from those reported by the earlier work of Borison and Wang, 1953 (reviewed by Wang, 1980). Their work suggested that increased heart rate was an autonomic correlate of nausea in animals. Increased heart rate was found compared to baseline during vomiting but decreased heart rate characterised the time of nausea. There may be a different underlying mechanism for the expression of this in animals versus humans. It is another example of how an animal model of nausea may not be applicable to human nausea (Morrow, 1984; Redd *et al.*, 1991).

Data are further consistent with the hypothesis that nausea is associated less with the relaxation of a sympathetic drive as with a rebound of parasympathetic tone. The degree to which these two potentially competing mechanisms set up a mutual tension is a basis for some speculation.

Autonomic variables changed differentially during periods of chemotherapy induced nausea and emesis compared to a non-drug baseline; furthermore, there appeared to be a different time course by which they changed during the expression of peak nausea. Variables dealing with sympathetic activity seemed to change further in time from an initial emetic episode. Those variables dealing primarily with parasympathetic effects such as heart rate decrease were found to occur closer to the time of emesis.

The different patterns of responding for nausea and emesis are not consistent with the suggestion that nausea and emesis are tightly coupled and that they are two components of the same reflex (Carpenter, 1990). They suggest rather that nausea may have the same underlying sequential activation that Davis, *et al.*, 1986, have proposed as an explanation for emesis. The view of this model is that responses may proceed through a series of sequential steps. The finding that there was variation in the time at which the variables changed prior to emesis is consistent with this type of a model.

These data support the view that vomiting is not simply more intense expression of the variables than is nausea. A different pattern was shown where heart rate and blood volume pulse decreased from baseline during nausea but increased during vomiting. Temperature and pallor showed roughly a linear increase from a one hour period of nausea to a one hour period of vomiting. This different pattern may

reflect different underlying mechanisms between the two symptoms.

Extension of this measurement methodology to other clinical situations may yield useful comparisons. For example, similar findings from pregnancy induced nausea and vomiting would support a common underlying mechanism of nausea. Examination of nausea and vomiting caused by different chemotherapy agents or anaesthetic agents with varied emetic potential would also help explore whether results reported here are singular or support a more generalisable mechanism.

Support for the development of the physiological monitoring equipment was provided, in part, by a Research Career Development Award KO4-CAO1038 from NCI DHHS, and grant RO1-NR01905 from the National Center for Nursing Research DHHS. The physiological monitoring equipment was designed by Dr Oman of MIT and fabricated by Mr Cook of MIT.

The author thanks Drs, Bill Redd and Paul Jacobs who provided helpful critiques and Barbara Cichetti who typed the manuscript.

References

COLTON, T. (1974). *Statistics in Medicine*. Little Brown & Company, Boston.

COWINGS, P.S., NAIFEH, K.H. & TOSCANO, W.B. (1990). The stability of individual patterns of autonomic response to motion sickness stimulation. *Aviation & Space Environ. Med.*, **61**, 399–405.

COWINGS, P.S., SUTER, S., TOSCANO, W.B., KAMIYA, J. & NAIFEH, K. (1986). General autonomic components of motion sickness. *Psychophysiology*, **23**, 542–551.

CARPENTER, D.O. (1990). Neuro-mechanisms of emesis. *Can. J. Physiol. Pharmacol.*, **68**, 230–236.

DAVIS, C.J., HARDING, R.L., LESLIE, R.A. & ANDREWS, P.L.R. (1986). The organization of vomiting as a protective reflex. In nausea and vomiting: Mechanism and Treatment. Davis, C.J., Lake-Bakaar, G.V., Grahame-Smith, D.J. (eds) pp. 65–75. Berlin, Heidelberg: Springer-Verlag.

DOBKIN, P.L. & MORROW, G.R. (1986). Biopsychosocial assessments of cancer patients: Methods and suggestions. *Hospice J.*, **2**, 37–61.

GRAHAM, D.T., KABLER, J.D. & LUNGSFORD, L. (1961). Vasovagal fainting: a diphasic response. *Psychosomatic Med.*, **23**, 493–507.

GUYTON, A.C. (1976). *Text Book of Medical Physiology*. Philadelphia: W.B. Sanders Company.

HARDING, R.K. (1990). Concepts and conflicts in the mechanism of emesis *Can J. Physiol. Pharmacol.*, **69**, 218–221.

MARTIN, M. (1991). Myths of antiemetic treatment. Br. J. Cancer, (in press.)

MONEY, K.E. (1970). Motion sickness. *Physiol. Rev.*, **50**, 1–39.

MORROW, G.R., BLACK, P.M. & DUDGEON, D.J. (1991). Advances in data assessment: Application to the etiology of nausea reported during chemotherapy, concerns about significance testing, and opportunities in clinical trials. *Cancer*, **67**, 780–787.

MORROW, G.R. (1985). The effect of the susceptibility to motion sickness on the side effects of cancer chemotherapy. *Cancer*, **55**, 2766–2770.

MORROW, G.R. (1984). The assessment of nausea and vomiting: Past problems current issues, and suggestions for future research. *Cancer*, **53**, 2267–2280.

OMAN, C.M. & COOK, W.J.C. *Dynamics of skin pallor in motion sickness as measured using an infrared reflectance technique*. 54th Annual Aerospace Medical Association Meeting, Houston, Tx., May, 1983.

OMAN, C.M., LICHTENBERG, B.K. & MOONEY, K.E. (1984). *Space motion sickness monitoring experiment: Space Lab 1*. Paper presentation, NATO-AGARD Aerospace Medical Panel Symposium, Williamsburg, Virgina, May, 1984.

OMAN, C.M. (1990). Motion sickness: A synthesis and evaluation of the sensory conflict theory. *Can. J. Physiol. Pharmacol.*, **68**, 294–303.

REDD, W.H., SILBERFARB, P.M., ANDERSON, B.L. & 12 others (1991). Physiologic and psychobehavioral research in oncology. *Cancer*, **67**, 813–822.

SAKAI, F. & MEYERS, J.S. (1978). Regional cerebral hemodynamics during migraine and cluster headaches measured by the 133Xe inhalation method. *Headache*, **18**, 122–132.

TOSCANO, W.B., COWINGS, D.S. (1982). Reducing motion sickness: A comparison of autogenic-feedback training and an alternative task. *Aviation, Space & Environ. Med.*, 449–453.

WANG, S.C. (1980). *Physiology and pharmacology of the brain stem*. Futura, Mt. Kisco, New York.